CONTENTS

The American Journal of Medicine

VOL. VII NOVEMBER, 1949 No. 5

SYMPOSIUM ON DIABETES MELLITUS

Foreword . . . . . RUSSELL M. WILDER 569

Carbohydrate Metabolism . . . . . DEWITT STETTEN, JR. 571

Studies in Experimental Diabetes . . . . . R. E. HAIST 585

Association of Diabetes Mellitus and Disorders of the Anterior Pituitary, Thyroid and Adrenal Cortex . . . . WILLIAM M. BALFOUR AND RANDALL G. SPRAGUE 596

Pregnancy Complicating Diabetes . . . . . PRISCILLA WHITE 609

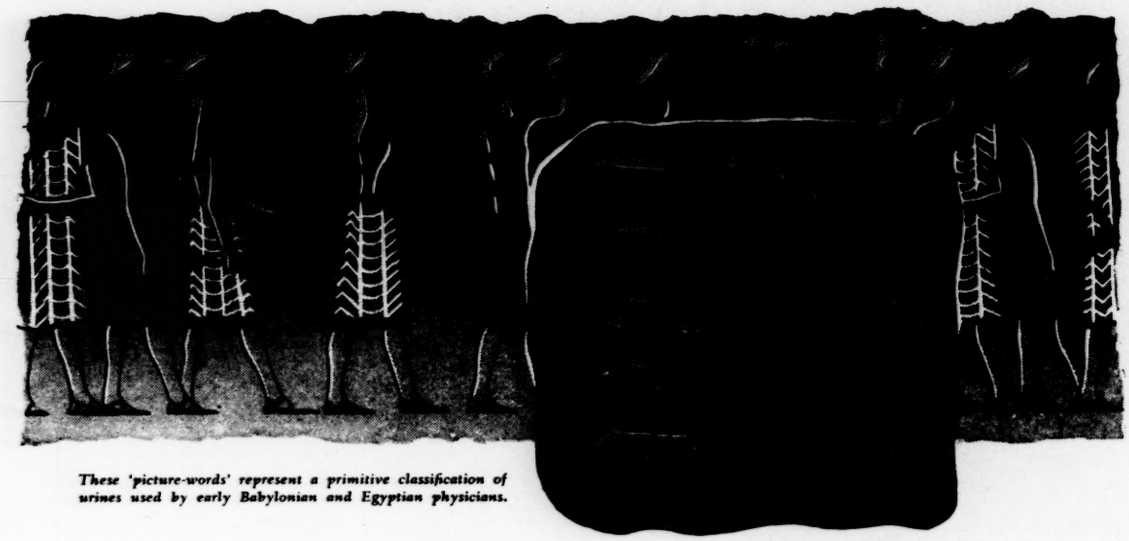
Arteriosclerosis and Diabetes . . . . . JOSEPH H. BARACH 617

Management of Diabetes in a General Medical Practice RUSSELL M. WILDER, JR. 625

Diabetic Coma. Metabolic Derangements and Principles for Corrective Therapy GEORGE M. GUEST 630

In designing this Symposium on Diabetes Mellitus Dr. Wilder has had in view the needs of a general medical audience rather than those of the specialist concerned largely with details of management. The papers, therefore, present the problem in its broad aspects. The contributors, each especially well qualified, have labored conscientiously to present their points of view lucidly and effectively. Careful study of these exercises will give the reader insight and perspective in this field.

Contents continued on page 5



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CONTENTS

The American Journal of Medicine

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Contents continued from page 3

Clinical Studies

Changes in the Volume of the Plasma, Interstitial and Intracellular Fluid Spaces During Hydration and Dehydration in Normal and Edematous Subjects

SAMUEL E. LEARD AND EDWARD D. FREIS 647

A lucid study of the effect of hydration and dehydration on shifts in the several fluid compartments in normal and edematous subjects. Limitations in the use of hematocrit and plasma protein determinations as a measure of plasma volume are pointed out.

Insulin Mixtures. Experiences in the Use of Extemporaneous Bottle Mixtures in Diabetic Clinic Patients

BERT H. WIESEL, A. BANKSTON RISER AND STANLEY S. KAHN 655

An analysis of the use of insulin mixtures in sixty-seven diabetics, with special reference to problems in clinic care.

Review

Cardiac Complications of Diabetes Mellitus

IRVING M. LIEBOW AND HERMAN K. HELLERSTEIN 660

The authors consider the incidence of coronary arteriosclerosis in diabetics, the role of cardiovascular collapse and of hypopotassemia in acidosis, the effect of insulin reactions in elderly diabetics.

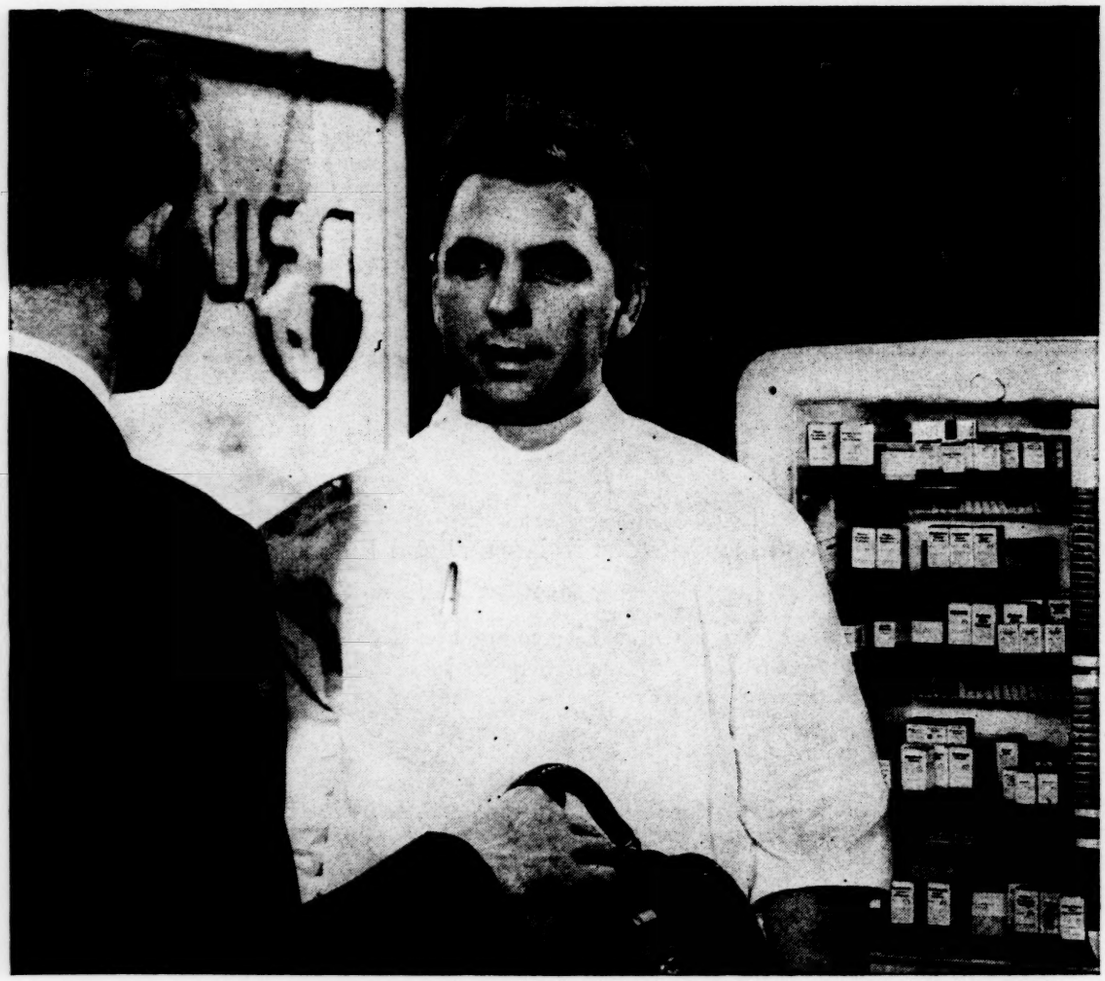
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Chloramphenicol (Chloromycetin) in the Treatment of Infectious Diseases

JOSEPH E. SMADEL 671

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Contents continued on page 7



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CONTENTS

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VOL. VII NOVEMBER, 1949 No. 5

Contents continued from page 5

Case Reports

Tetanus Following Dental Extraction DWIGHT GRISWOLD AND ALBERT C. HERRING 686

A case of tetanus with interesting implications.

Loeffler's Syndrome with Associated Eosinophilic Polyserositis
HELEN A. DICKIE AND ELIZABETH GRIMM 690

A well studied case illustrating certain complications of bronchial asthma that probably occur more frequently than is appreciated.

Kala-azar. With Special Studies of Bone Marrow and Lymph Nodes
WILLIAM J. SENTER, HAROLD SUTKER AND HORTENSE ELTON GARVER 694

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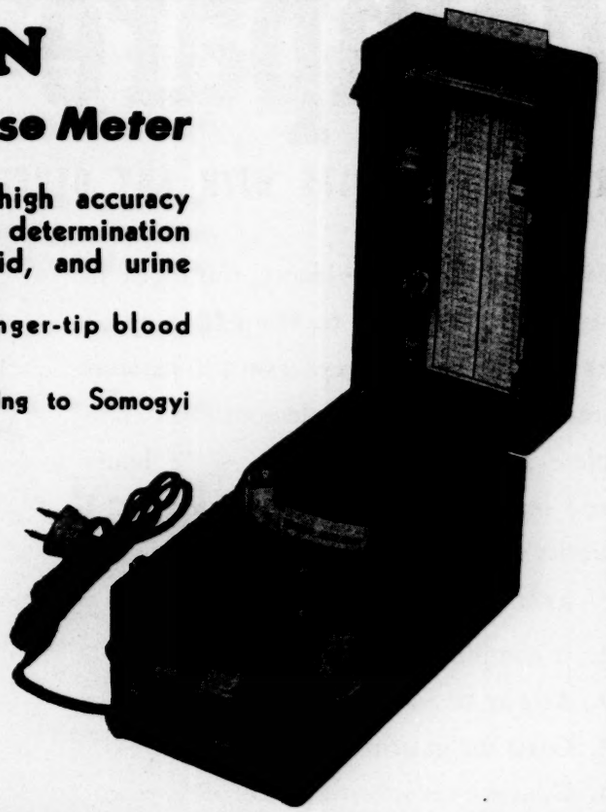
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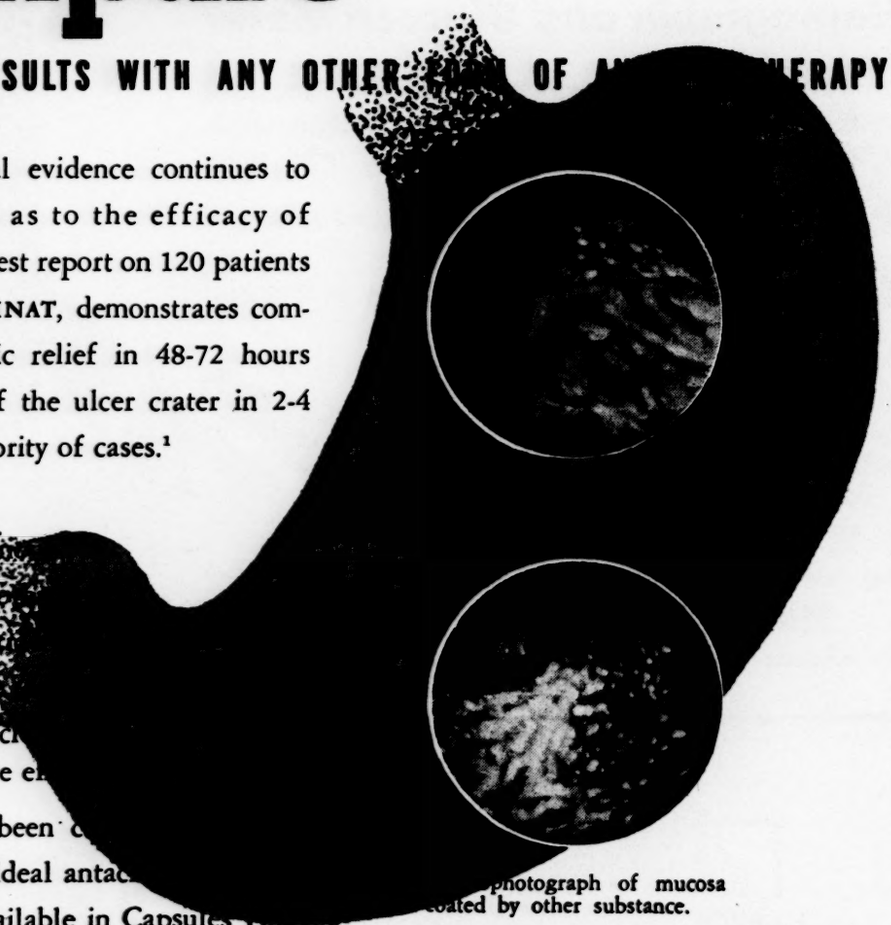
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Weiss, S., Espinal, R.B. & Weiss, J.: Therapeutic Application of Anion Exchange Resins in the Treatment of Peptic Ulcer, Review of Gastroenterology, 16:501-509, June, 1949.

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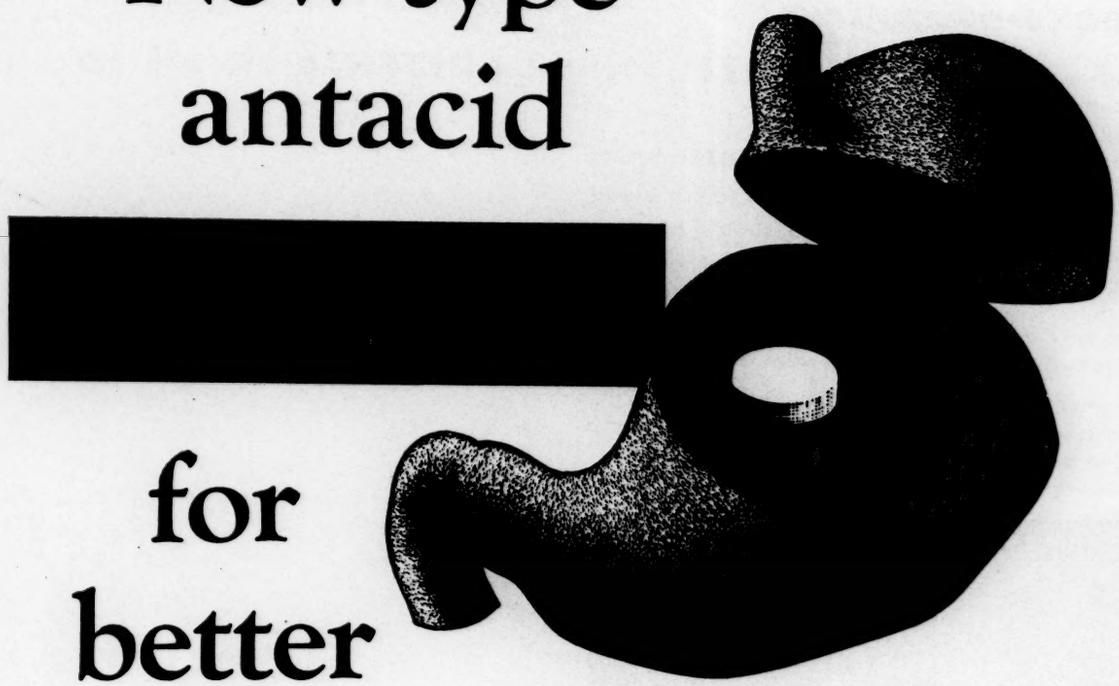
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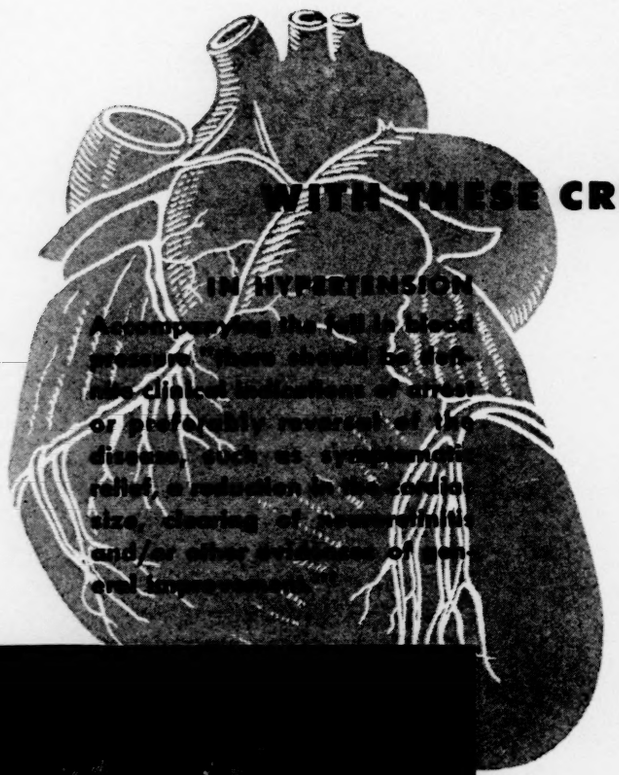
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1. Brick, I.B.: Amer. J. Dig. Dis., *In Press* 2. Bralow, Spellberg & Necheles: Scientific Exhibit #1112, A.M.A. Annual Session 1949



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1. Freis, E. D.: Med. Clin. N. Am. 32:1247-1258, 1948.
2. Freis, E. D., and Stanton, J. R.: Am. Heart J. 36:723-738, 1948.

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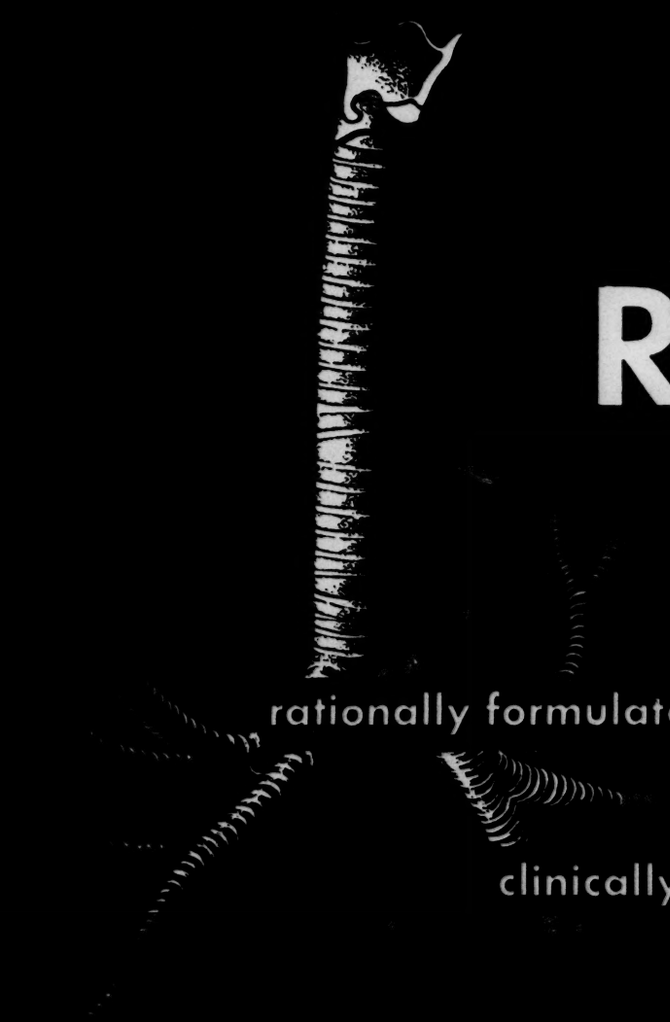
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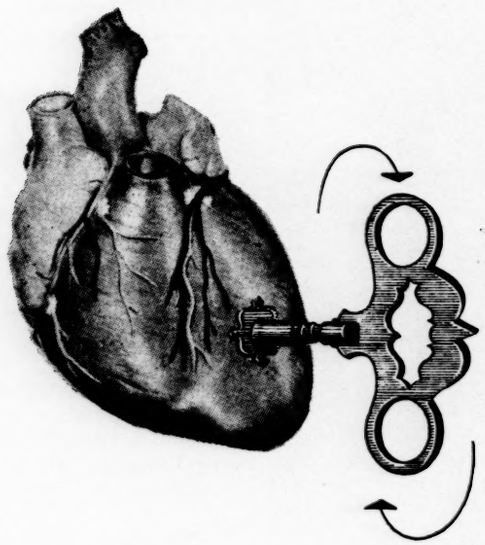
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SUPPLIED: Pint and gallon bottles.

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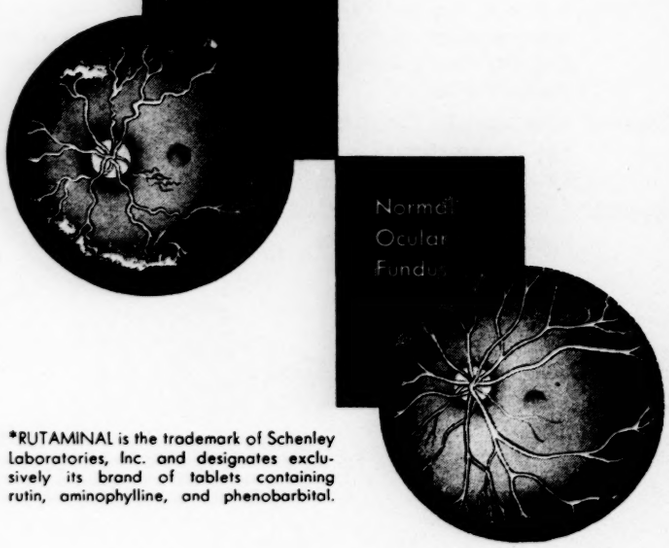
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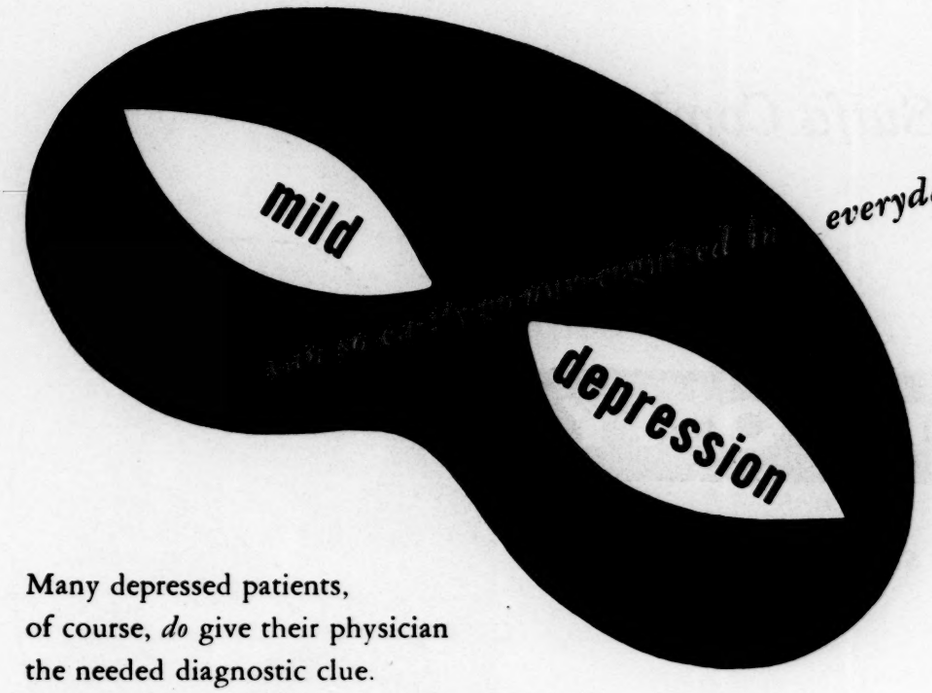
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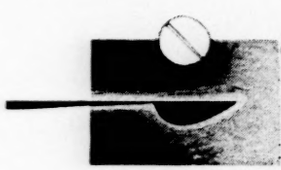
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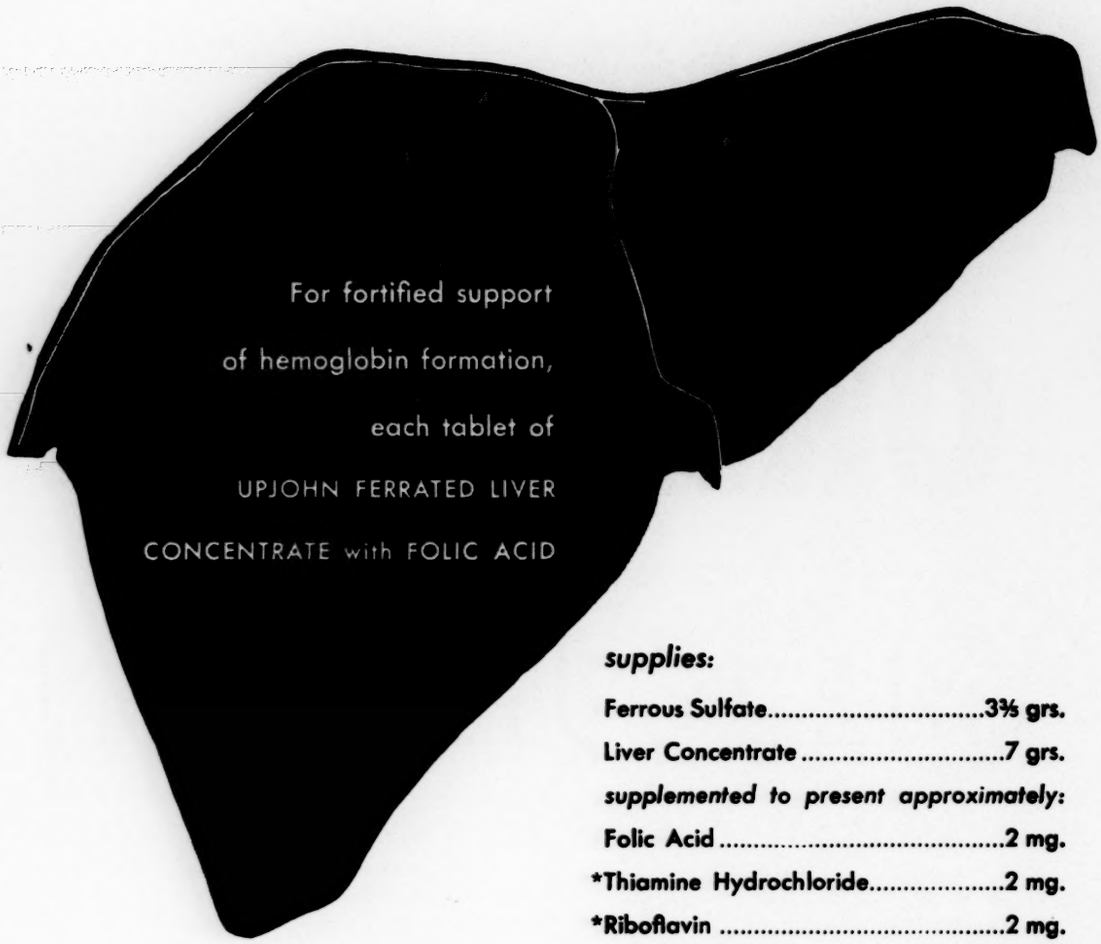
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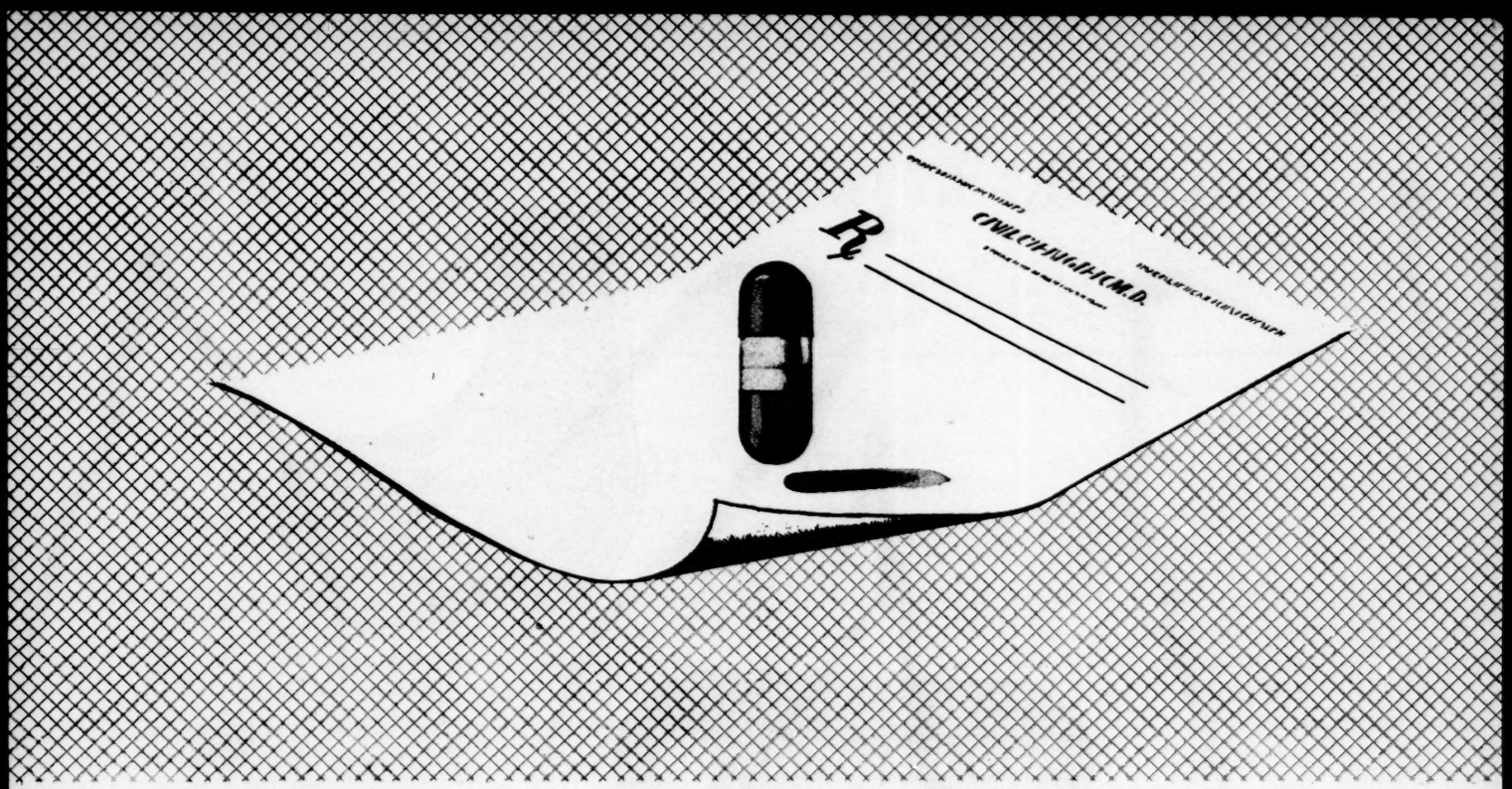
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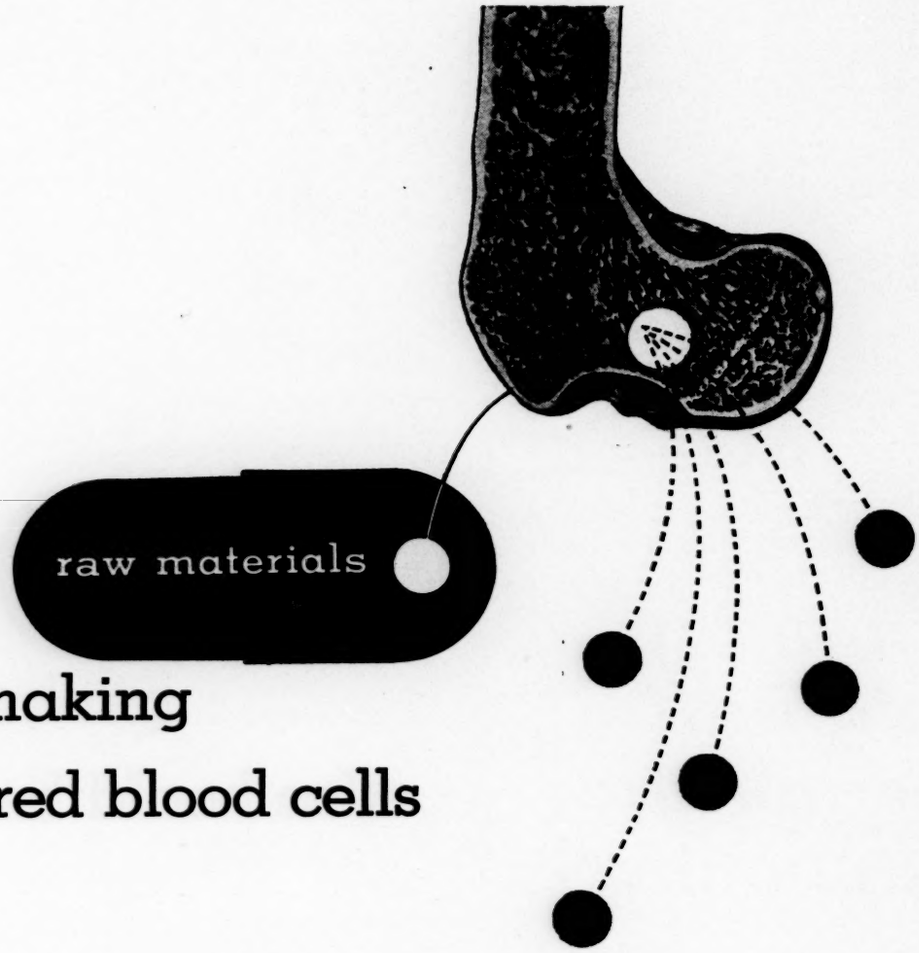
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The American Journal of Medicine

VOL. VII NOVEMBER, 1949 No. 5

Foreword

DIABETES MELLITUS, for good reasons, has attracted the attention of outstanding investigators in many fields of medicine. In the first place, this disease is a health hazard of major significance. Data on the incidence of the disease have been published but for the most part are difficult to assess. A reasonable estimate, however, is that the population of the United States includes not less than 1,000,000 diabetic persons, and many have believed that the incidence of the disease has increased in recent years and may still be increasing.

For a long period we have kept a separate yearly count of the new cases of diabetes seen at the Mayo Clinic, and of the return patients treated for diabetes at some previous time in the clinic. We have related the number of new cases of diabetes year by year to the total number of new patients who registered for examination in the clinic in the corresponding years, arriving thus at a *new case rate index*. Admittedly, this index is not the literal equivalent of the incidence of the disease in, or the case rate of, the population. The latter could be obtained only if all cases of diabetes were detected and their number divided by the population, which up to now has not been possible. However, the index can be accepted as a reasonable barometer of changes in the case rate of the population because any important increase or decrease in the incidence of diabetes in any given year in the population from which are drawn the patients of the clinic very likely would be reflected in a corresponding change in the incidence of new diabetic patients coming to the clinic. With this thought in mind, changes in the new case rate index over the years are worthy of notice. The index in 1920 was 0.62 per cent; it was 1.05 per cent in 1925; 1.24 per cent in 1930; 1.60 per cent in 1935 and 2 per cent in 1941. Since 1941 it has remained in the neighborhood of 2 per cent. In 1948 there were 1,375 new diabetic patients; of this number 329 had been seen in the clinic in earlier years but had not given evidence of diabetes at previous examinations. Of interest is the fact that the disease in 50.2 per cent of these new patients was severe enough to necessitate the use of insulin. Also of some significance is the fact that for every five new patients who knew they had diabetes when they came to the clinic, another instance of diabetes was discovered among patients in the clinic who when they registered had not suspected that they had diabetes.

The increase between 1920 and 1941 in the new case rate index for diabetes in the Mayo Clinic is not to be explained by the discovery of insulin in 1920 and the consequent increasing interest in the detection of diabetes. Relatively few of the patients who come to the clinic do so because of diabetes, and the reliability of the detection of diabetes in the clinic has not changed since 1920. For every patient registering since that year, and before, urinalysis has been performed and, with few exceptions, when glycosuria has been detected the level of blood sugar has been determined; a fasting blood sugar determination first and when uncertainty remained, a glucose tolerance test. The figures I have quoted relate only

to new patients for whom a diagnosis of diabetes mellitus was based on the finding of abnormally high blood sugar levels; therefore, from the data given the inference is clear that in the population from which the patients of the clinic are drawn the incidence of diabetes between 1920 and 1941 was multiplied by three or more, also that since 1941 there has been no further increase. The stabilization of the new case rate index since 1941 is reassuring; nevertheless, the incidence of diabetes obviously is of such magnitude as to call for major efforts in detecting the disease and in its treatment.

Another reason for the widespread interest in diabetes mellitus is that this disease affords unusual opportunities for study of the machinery of metabolism. It opens a door, so to speak, and thereby provides a view of what is going on inside. Dextrorotatory glucose appears in the urine. The explanation came with von Mehring's and Minkowski's discovery in 1889 that ablation of the pancreas provoked diabetes. The interest thus aroused culminated in the separation of insulin from the pancreas by Banting and Best in 1920, and in the discovery by them of the usefulness of insulin in the treatment of experimental pancreatic diabetes and the diabetes mellitus of man.

Failure to utilize D-glucose, when the failure is severe, leads to accumulation in the body of aceto-acetic acid, hydroxybutyric acid and acetone. An alkali deficit results from this accumulation of organic acids. Study of the chemical disturbances which bring all this about has thrown some light on the normal metabolism of fats and proteins, and the long series of investigations of diabetic acidosis, initiated by Hallervorden, Stadelmann and Minkowski, students of Naunyn in Königsberg, Germany, in the 1880's, has resulted in the ever growing body of knowledge about this most immediate hazard of diabetes mellitus.

Finally, in more recent years some understanding has been gained of the parts played in the metabolism of carbohydrate by the pituitary and adrenal glands. This stems mainly from Houssay's and Biasotti's brilliant finding in 1930 that pancreatic diabetes could be modified profoundly by ablation of the pituitary gland. Most recently additional advance has been promoted through the isolation in relatively pure form of many of the hormones of the anterior lobe of the pituitary body and of the cortex of the adrenal gland.

In the symposium on diabetes mellitus which follows we are indebted to Dr. Stetten for a clear interpretation of current views about the fate of D-glucose in metabolism; to Dr. Haist for reviewing the contributions to knowledge of diabetes mellitus which have come from experimental diabetes; to Dr. Balfour and Dr. Sprague for clinical reports of cases of human diabetes in which endocrine glands other than the pancreatic islands were importantly involved; to Dr. White for sharing with us her large experience with the problem of pregnancy in diabetes; to Dr. Barach for his views on what now appears to be the major threat in diabetes, premature sclerosis of the vascular tree; to Dr. Wilder, Jr., for reflections on the problem presented to the nonspecialists in diabetes who must assume responsibility for the care of a large proportion of the diabetic population; and finally to Dr. Guest for a discussion of procedures currently employed in treating diabetic acidosis.

The subjects covered in these papers are in fields which at present are undergoing energetic cultivation. The material, much of it at least, is not as yet in textbooks. The purpose back of this symposium is to bring us up to date in these several major aspects of diabetes mellitus.

RUSSELL M. WILDER, M.D.

Symposium on Diabetes Mellitus

Carbohydrate Metabolism*

DeWitt Stetten, Jr., M.D.
New York, New York

ENERGY CONSIDERATIONS

Many of the individual processes which, when taken together comprise the normal body economy, when considered as isolated systems prove to be endergonic, that is, energy-consuming processes, incapable of continued operation unless the needed energy is supplied in one or another fashion. By way of preface to a discussion of the role of carbohydrates in the total mammalian metabolism it may be well to tabulate some of these endergonic processes in order that insight may be gained into the disposition of the relatively enormous amounts of energy that the normal organism derives from the breakdown of carbohydrates each day: (*a*) the maintenance of body temperature at a level in general above that of the environment, (*b*) the performance of mechanical work, both voluntary and involuntary, incident to muscle contraction, (*c*) the initiation and transmission of neural impulses, (*d*) the secretion or reabsorption of tissue and blood constituents, often against a concentration gradient, and (*e*) the continuous regeneration of the large molecules of protein, polysaccharide and fat, which make up the major portion of the organic components of protoplasm, for the synthesis of which not only the small building stones but also a supply of energy is needed.

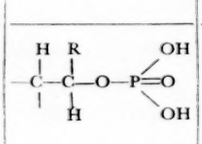
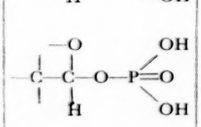
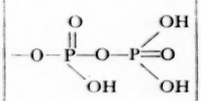
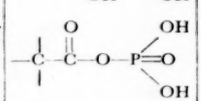
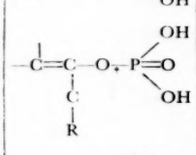
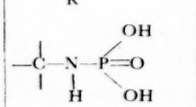
These and other processes are continuously consuming energy, and this energy deficit must ultimately be met by the caloric supply of the diet if the organism is to remain in balance. The incidental energy requirements of growth, pregnancy, lactation, tissue repair and wound healing must also be derived from this source, and in view of the fact that in a perfectly normal dietary well over half of the calories of the diet may appear in the form of carbohydrate, it is of obvious importance to understand what little is known of the means whereby the energy, made available to the organism by the breakdown of carbohydrate, is delivered to these various energy-consuming processes.

The primitive idea that sugar is burned in the animal body as it might be burned in a furnace and that the heat liberated thereby is the source of energy for muscle work has long been recognized as untenable. The efficiency of the transfer of usable energy through the mode of heat is limited by the fraction $\frac{\textit{temperature difference}}{\textit{absolute temperature}}$ and such processes become efficient only when a large temperature difference can be achieved. Thus, at body temperature, assuming a thermal difference of 10°c to occur, no more than one thirtieth of the energy liberated by the combustion of sugar would be available for the performance of useful work. Yet isolated muscle has been shown to operate on a nutrient of glucose with vastly greater efficiency than 3 per cent despite the fact that no significant thermal differences within the muscle have been shown to occur. From this it follows that a large portion of the energy liberated by the breakdown of glucose in the mammalian cell must be delivered to systems capable of accepting energy and transforming it into useful work without the intervention of the energy-mode of heat. Recognition of this fact gave rise to the conceptof "energy-linked processes" wherein

* From the Division of Nutrition and Physiology, The Public Health Research Institute of The City of New York, Inc., N .Y.

the energy released by one reaction is immediately accepted and utilized by some other reaction occurring simultaneously. After a generation of exploration one may now point to one such energy link, which has clearly been proved to be operative in

TYPES OF COMPOUNDS OF PHOSPHORIC ACID

Type	Structure	Energy of Hydrolysis	Examples
Phosphoric ester of simple alcohol		Low	Glucose-6-phosphate; 3-phosphoglyceraldehyde 2-phosphoglyceric acid
Phosphoric acid acetal		Low	Glucose-1-phosphate; 1,3-diphosphoglyceraldehyde (the 1-phosphate)
Anhydride of phosphoric acid		High	Adenosine triphosphate; adenosine diphosphate
Mixed anhydride of phosphoric acid		High	Acetyl phosphate; 1,3-diphosphoglyceric acid (the 1-phosphate)
Enol phosphate		High	Phosphopyruvic acid
N-substituted phosphamic acid		High	Phosphocreatine; phosphoarginine

biologic systems and which must serve as an example of the devices which have evolved to accomplish the necessary energy transfer.

The biologically important compounds of phosphoric acid[1] have been shown to fall roughly into two groups, and this division is based on the amount of energy which is released when these compounds are subjected to hydrolysis. If one considers the reaction type:

$$(1)\ ROPO_3H_2 + H_2O \rightarrow ROH + H_3PO_4 + \Delta E$$

where ΔE is the energy released, one sees that of some compounds of phosphoric acid, the quantity ΔE is small, and, intimately associated with this fact, the hydrolysis as written is readily reversible and the possibility exists that the compound may arise and accumulate to an appreciable extent as a result of spontaneous synthesis from its parts. Such compounds are said to contain "low energy phosphate." There are, on the other hand, numerous compounds of phosphoric acid which, when subjected to hydrolysis, yield large amounts of energy; in regard to the foregoing equation, ΔE is a large quantity. The hydrolysis of such compounds proceeds essentially irreversibly and completely, and such compounds cannot be pictured as arising to any appreciable extent from spontaneous interaction of the products of hydrolysis. These compounds are referred to as "high-energy phosphate" compounds.

Included in the table are examples of these two types of compounds of phosphoric acid. In relation to this table, it should be pointed out that it is thermodynamically possible for any compound of high energy to surrender its phosphate residue to some acceptor and generate a phospho-compound of low energy, whereas the reverse cannot occur. An example of a reaction of this type is the well known hexokinase-catalyzed phosphorylation of glucose:

(2) glucose + adenosine triphosphate → glucose-6-phosphate + adenosine diphosphate

Here a low-energy phosphate bond has been established at the expense of a high-energy bond.

Of the several high energy compounds listed in the table, by way of generalization it may be stated that the energies of hydrolysis of all of these compounds are of the same order of magnitude. This fact gives rise to the thermodynamic possibility of the generation of a new high energy phosphate bond at the expense of another high energy bond, and, furthermore, since the net gain or loss of energy in such a reaction will be small, such a reaction may be expected to proceed reversibly. Examples are given herewith:

(3) phosphopyruvic acid
+ adenosine diphosphate ⇄ pyruvic acid
+ adenosine triphosphate
(4) phosphocreatine
+ adenosine diphosphate ⇄ creatine
+ adenosine triphosphate

The energy link believed to intervene between the catabolism of glucose, on the one hand, and the contraction of muscle, on the other, is closely related to such shuttling about of high energy phosphate. The current picture describes the contractile unit of the myofibril as existing in two states, an extended and a contracted state. In the extended or elongated condition, it is rich in potential energy, like an extended spring. As it contracts, with the generation of kinetic energy, it loses potential energy, precisely as is the case with a stretched spring that is permitted to contract, and before it can do any more work, it must be recharged with energy and reconverted to the extended condition. This transformation is apparently accompanied with and closely related to the introduction, into the myosin unit, of phosphate, and, what is of importance to the present discussion, the phosphate required is of the high energy variety. The continuous operation of a muscle fiber may be pictured as being made up of two alternating phases: extension, accompanied by an increase in potential energy and the coincident introduction of high energy phosphate at the expense of some high energy phosphate compound in the vicinity; and contraction, accompanied by the performance of mechanical work on the environment, release of kinetic energy, decrease in potential energy and loss of phosphate as inorganic phosphate ions at an energy level of 0. Such a process may be repeated continuously as long as there is a supply of compounds of phosphoric acid of the energy-rich variety available in the neighborhood; in muscle tissue such a reservoir is at hand (Fig. 1). The terminal phosphoric acid residue of adenosine triphosphate appears to be the immediate source of high energy phosphate for the recharging of the contracted myofibril. Backing up this reservoir there is a second reservoir, in the form of the creatine phosphate which is abundant in striated muscle. By virtue of these reservoirs an isolated muscle may be made to undergo repeated

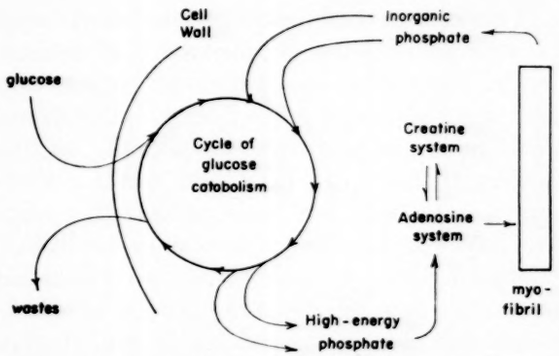


FIG. 1. The role of high energy phosphate in the transfer of energy from glucose catabolism to effector organ. (Adapted from Lipmann, F. In Nord, F. F. and Werkman, C. H. Advances in Enzymology. Vol. 1, p. 122, 1941.).

contractions even though carbohydrate catabolism may have been completely inhibited by the use of suitable poisons. Inevitably, however, in such a preparation, these reservoirs of high energy phosphate will soon be depleted, the high energy phosphate necessary to recharge the myofibrils will no longer be available and muscle work will come to a standstill.

It is at this point that the role of glucose catabolism in the working cell must be taken into account. One of the important consequences of the breakdown of glucose in the living cell is the generation of new high energy phosphate compounds in the formation of which glucose is catabolized and inorganic phosphate ions are consumed. Examples of individual reactions in which such high energy phosphate compounds arise will be given later in the text. Suffice it to state at this point that, per molecule of glucose degraded to pyruvate or lactate, two high energy phosphate bonds, according to current understanding, will have been created *de novo*. As the high energy phosphate which arises incident to the breakdown of glucose is transferable to

adenosine diphosphate, to regenerate adenosine triphosphate and secondarily creatine phosphate, the processes of normal glucose catabolism tend to offset the depletion of high energy phosphate stores that would otherwise result from continued muscle work.

This energy link between the breakdown of glucose and the performance of muscle work, involving the repeated generation and destruction of high energy phosphate, must not be supposed to be peculiar to this system. Indeed, at least one other endergonic process, the generation of polysaccharides, has been shown to be linked energetically to glucose breakdown through the same type of shuttling about of phosphate residues (discussed later), and it may be supposed that other energy-consuming processes operate, in the cell which is destroying glucose, by virtue of this same energy link. It must, however, be borne in mind that energy links in addition to the one described may yet be unearthed, and, indeed, at the present time one is able, by reactions known to occur, to account for the disposition of only a small fraction of the energy liberated in the complete oxidation of glucose to carbon dioxide and water.

SOURCES OF GLUCOSE

The glucose on which the cells of the mammalian organism depend, to a greater or lesser extent, for their continued nutrition is of course the glucose dissolved in the extracellular fluids of the body, of which the blood plasma may be taken as representative. Whereas it is undoubtedly true that some mammalian cells retain a vestigial capacity to assimilate carbon dioxide,[2] the mammal is obviously incapable of synthesizing its full supplement of glucose from carbon dioxide and water, a synthesis that is effectively carried out by certain microorganisms and chlorophyll-containing plants. There are three sources of blood glucose that come into consideration, and of these the most important one quantitatively is the carbohydrate of the diet. The other contributions to the blood glucose may be classified under the headings of glycogenolysis and gluconeogenesis.

The carbohydrates of the diet that are of nutritional significance are surprisingly few in number (Fig. 2). Only three monosaccharides, glucose, fructose and galactose, need be mentioned, and although the first two of these do occur as such in various fruits, it is questionable whether any of these three ever comprises a major portion of a normal diet. Of the disaccharides, sucrose, the common sugar of cane and beet, is of course a variable dietary component, and lactose, the carbohydrate of milk, is obviously of significance in infant nutrition. Maltose is of interest not so much as a naturally occurring product but rather as an intermediate in the breakdown of larger polysaccharide molecules. The hydrolysis of each of these disaccharides gives rise to a pair of monosaccharide molecules:

(5) sucrose → glucose + fructose
(6) lactose → glucose + galactose
(7) maltose → glucose + glucose

The major portion of the usual dietary carbohydrate is made up of polysaccharides, compounds of large and imperfectly known molecular size. The starches, of vegetable origin, and glycogen, of animal origin, are the important members of this group, and both are made up of glucose fragments linked to each other in what is termed "glucosidic linkage," in which the number 1 carbon of one glucose unit is coupled, through an oxygen bridge, to the number 4 or number 6 carbon of an adjacent glucose unit. On complete hydrolysis of these materials the sole carbohydrate obtained is glucose.

The remaining carbohydrates of the diet are of little nutritional importance. The pentoses, such as xylose and arabinose, which may be present in the diet to a scant extent, are known to be absorbed across the intestinal mucosa much more slowly than the common hexoses, and little is known of their further metabolic utilization. Polysaccharides which on hydrolysis yield pentoses are represented among the gums, such

as gum arabic and acacia, as well as agar, but these are not digested or absorbed and serve merely to increase the bulk of the intestinal contents. Similarly cellulose, a polysaccharide of glucose, although apparently digested by certain ruminants, is not subject to digestion in the human gastrointestinal tract and serves only as roughage.

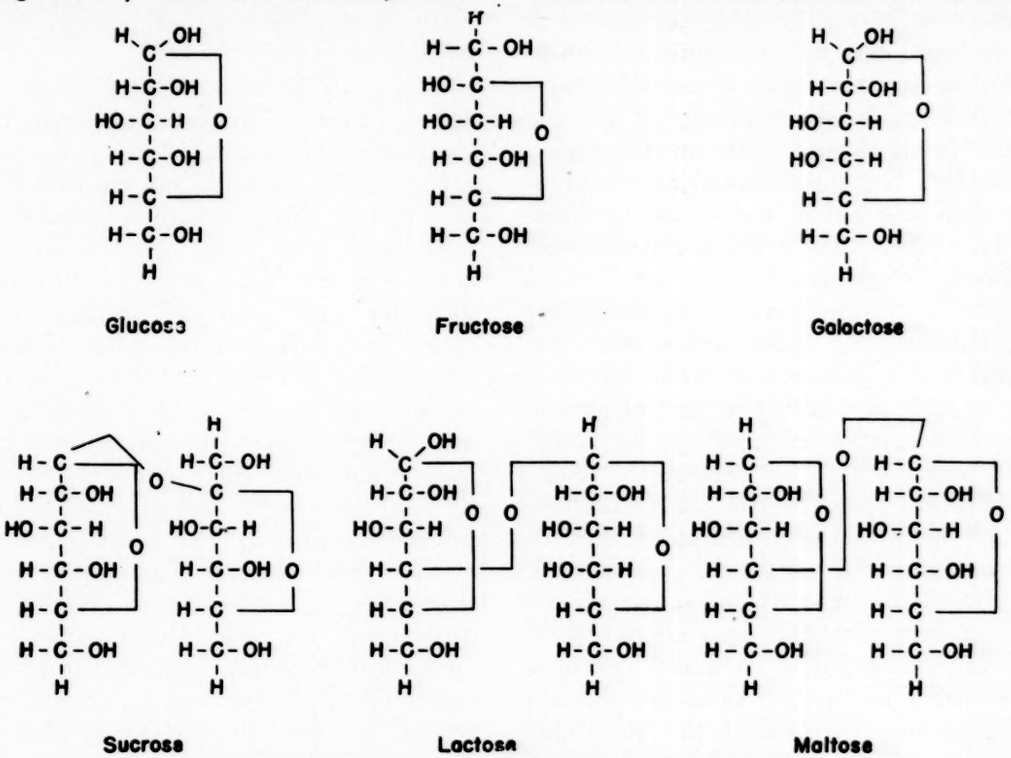


FIG. 2. Formulas of the nutritionally important sugars.

The digestion of carbohydrates, like the digestion of proteins and fats, may be described as a series of enzyme-catalyzed hydrolyses in which the large molecules of the diet are broken down to smaller unit fragments preparatory to their absorption. It is generally believed that the bulk of dietary carbohydrate is degraded to the monosaccharide level prior to absorption, although small amounts of disaccharide, such as sucrose, may be absorbed without hydrolysis. The first of the enzymes, in the most general sense glucosidases, to operate on ingested polysaccharide is the salivary amylase, ptyalin. In view of the short duration of contact between dietary polysaccharide and active ptyalin, the extent of digestion accomplished by this enzyme is probably small. When the bolus of food enters the stomach, ptyalin is rapidly inactivated by the acidic environment which it encounters, so that enzymic digestion comes to a standstill. A small degree of digestion in the stomach incident to the catalysis of hydrogen ions has been postulated.

The small intestine is the major site both of polysaccharide digestion and of absorption of the resultant simple sugars. Pancreatic amylase and the glucosidases of the succus entericus both participate in catalyzing the hydrolysis of glucosidic links and the ultimate disintegration of the complex sugars of the diet to the monosaccharide level.

Derived from the carbohydrates of the diet one may expect to see in the lumen of the small intestine a mixture of glucose, fructose and galactose, and, except for that portion which undergoes bacterial fermentation, these monosaccharides are delivered to the portal bloodstream in a quantitative

fashion. The transport of these hexose molecules across the intestinal mucosa appears not to be simply a matter of diffusion, since the rate of this transport is in general independent of the concentration gradient against which it is operating. It appears to be a vital process, dependent in some fashion on the reaction of phosphorylation and probably is not dissimilar to the process of reabsorption of glucose from the renal tubule. The several sugars are absorbed from the intestinal canal at widely differing rates, the order of these rates being: galactose > glucose > fructose > mannose > pentoses.[3]

Glucose is certainly the most abundant hexose entering the bloodstream from the intestinal tract. Galactose and fructose, insofar as they are absorbed and enter the processes of glycolysis and glycogenesis, may be presumed to be capable of ready transformation into the glucose configuration. Of the various monosaccharides of metabolic interest, galactose is formed abundantly and excreted as lactose in the process of lactation and also crops up as the characteristic sugar in many cerebrosides; ribose and desoxyribose are formed from unknown precursors in the body and appear in the nucleic acids and nucleotides, and xyloketose appears as a urinary constituent in pentosuria. From the nutritional point of view, however, the concern is predominantly with glucose.

In addition to the absorption of the products of carbohydrate digestion from the intestinal canal, there are two other types of processes which contribute to the blood glucose, and these are conveniently discussed under the headings of gluconeogenesis and glycogenolysis. Under the term gluconeogenesis may be included all reactions which originate with noncarbohydrate precursors and terminate with the generation of glucose. Among the materials which the body is capable of employing in this fashion are: (*a*) essentially all of the products that the body can generate from glucose down to and including the four-carbon dicarboxylic acids, (*b*) all of the amino acids that are capable of being transformed into or of contributing carbon atoms to any of the foregoing intermediates —such amino acids comprise the glucogenic amino acids—and (*c*) certainly glycerol and, according to some authorities, possibly the fatty acids, which may arise from the hydrolysis of fat.

Since, in general, the reactions of glycolysis, glucose breakdown, may proceed in both directions in the body, the products of glycolysis would be expected to be glucogenic. Certain of these products, however, may arise from other sources. Thus, α-ketoglutaric acid may be formed from glutamic acid and presumably from the other five-carbon amino acids as well, and oxaloacetic acid can certainly arise from the amino acid aspartic acid. The three-carbon amino acids, alanine, serine and cysteine may contribute their carbon skeletons to form pyruvic acid, and glycerol is similarly interconvertible in the body with certain of the three-carbon fragments that arise from the breakdown of glucose. When proceeding in the direction of glucose formation, these processes all funnel into the formation of glucose-6-phosphate. This compound, in common with other phosphorylated compounds, appears to cross cell membranes slowly, if at all, and is believed to be utilized for the most part in the very cells in which it is formed. The enzyme required for the catalysis of the irreversible hydrolysis of this product, perhaps a specific glucose-6-phosphatase:[3a]

(8) glucose-6-phosphate $\xrightarrow{\text{phosphatase}}$ glucose + phosphate ion

appears not to be uniformly distributed, and, while it is abundantly present in liver, it is lacking in striated muscle. Thus, whereas the liver is well able to contribute to the blood glucose as a result of gluconeogenic processes, such processes in muscle result in the augmentation of some other product, notably glycogen.

The third source of blood glucose to be considered is the breakdown of glycogen. This proceeds over well recognized steps:[4]

(9) glycogen + phosphate ion $\xrightleftharpoons{\text{phosphorylase}}$ glucose-1-phosphate

(10) glucose-1-phosphate $\xrightleftharpoons{\text{phosphoglucomutase}}$ glucose-6-phosphate

The glucose-6-phosphate which arises as a result of these reactions is, of course, subject to the same restrictions described, in that in liver, but not in muscle, it may be hydrolyzed to yield glucose (reaction 8). A consequence of this enzymic deficiency of striated muscle is the fact that muscle glycogen cannot contribute directly to the blood glucose, that the first products of glycogen breakdown in muscle that can escape readily from the muscle cell are pyruvic and lactic acids and that only as these do escape and are captured by the liver and employed there for gluconeogenesis can muscle glycogen contribute to the glucose of the blood.

GLYCOLYSIS

In summing up the sources of blood glucose, it may be pointed out that, in a quantitative sense, the breakdown of glycogen constitutes a much smaller contribution than do the other two processes and appears to be of major importance only in times of acute stress It should also be stressed that all three processes are undoubtedly operating continuously in the normal subject and this leads to a consideration of the fate, in the animal body, of the glucose thus made available. In the normal subject, essentially all of this glucose is consumed in one way or another, no appreciable amounts appearing in the excreta. Many metabolic pathways and many hypothetic intermediates have at one time or another come into consideration. The pathways and the intermediates presented herewith are those currently acceptable and well established experimentally, but should not be construed as the only possible routes over which glucose can be utilized. Rather should this scheme be considered as a highly probable series of reactions, which is believed to occur, with relatively minor modifications, in widely divergent types of cells, and which may serve as a model of the manner in which glucose is catabolized.[5]

The first step in the series (Fig. 3) appears to be the formation of glucose-6-phosphate from glucose by the irreversible, exergonic reaction:

(11) glucose + adenosine triphosphate $\xrightarrow{\text{hexokinase}}$ glucose-6-phosphate + adenosine diphosphate

It should be particularly noted that this reaction is not the reversal of the reaction whereby glucose-6-phosphate is hydrolyzed to glucose (reaction 8). The enzyme catalyzing the present reaction, in contrast to the phosphatase mentioned previously, appears to be ubiquitous, and this, the hexokinase reaction, would seem to occur in essentially all living cells. An important consequence of this reaction is that it converts the freely diffusing glucose into a phosphate which crosses membranes with difficulty and is thereby pictured as serving to capture glucose molecules in the intracellular compartment.[6] It has been suggested that it is by virtue of this mechanism of capture of glucose that the cells of the mammalian body are able to thrive on a predominantly glucose nutrient in spite of the fact that the concentration of glucose in the extracellular space is relatively low, in the neighborhood of 0.1 per cent.

Three possible fates of glucose-6-phosphate must next be considered. In the liver, but not in muscle, it may be hydrolyzed back to glucose by the action of phosphatase (reaction 8). Again, by the reversal of reaction 10 it may be transformed into glucose-1-phosphate, and from this product a wide variety of cells are able to form glycogen. This latter reaction has been shown to require the same phosphorylase which was involved in the breakdown of glycogen (reaction 9) and, in addition, a small seed of glycogen or some similar polysaccharide to initiate the coupling of one glucose fragment to another. In the course of this

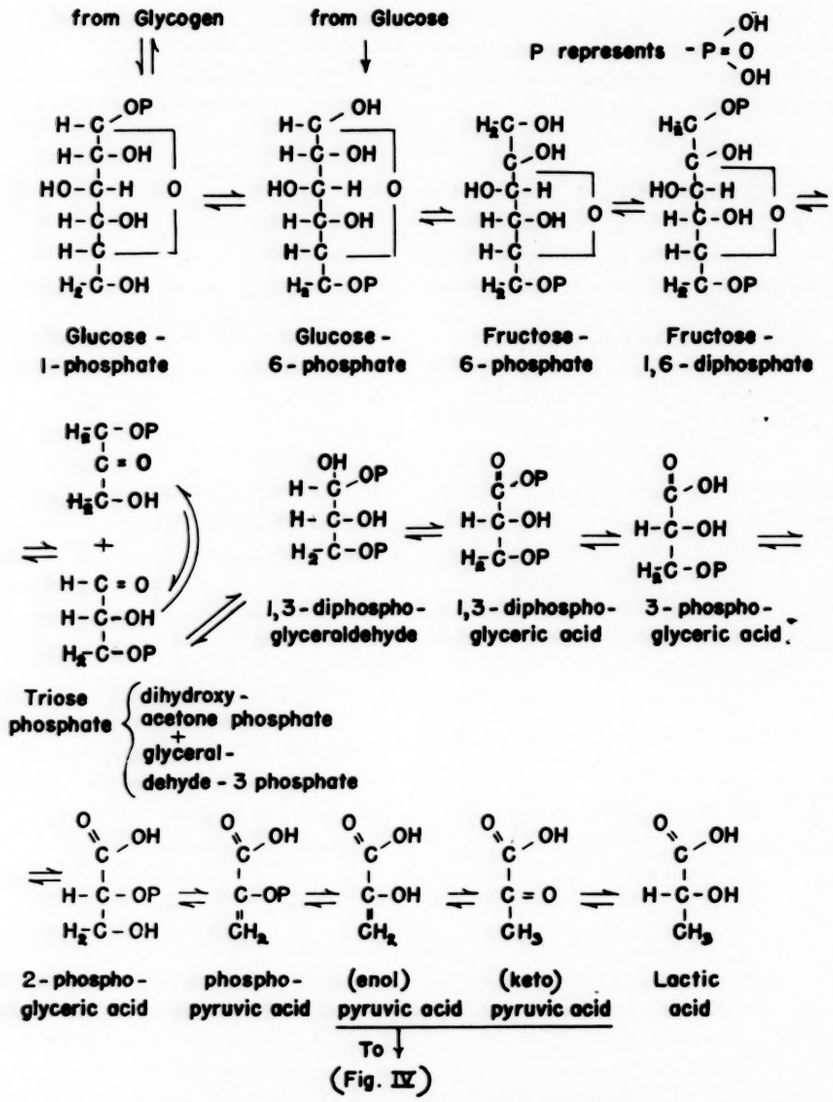


FIG. 3. The pathway of anaerobic glycolysis.

reaction phosphate ion is eliminated. The third fate of glucose-6-phosphate is its transformation to fructose-6-phosphate, a reversible reaction:

(12) glucose-6-phosphate $\overset{\text{isomerase}}{\rightleftharpoons}$ fructose-6-phosphate,

and since the same product may arise from fructose, by the reaction:

(13) fructose + adenosine triphosphate $\xrightarrow{\text{hexokinase}}$ fructose-6-phosphate + adenosine diphosphate

it may be considered that it is at this point that the metabolisms of glucose and of fructose merge.

Fructose-6-phosphate now acquires a second phosphate in the number 1 position by the reaction:

(14) fructose-6-phosphate + adenosine triphosphate $\xrightarrow{\text{phosphohexokinase}}$ fructose-1,6-diphosphate + adenosine diphosphate,

and the resulting product, loaded at both ends, undergoes cleavage at the midpoint to yield a mixture of the two triose phosphates:

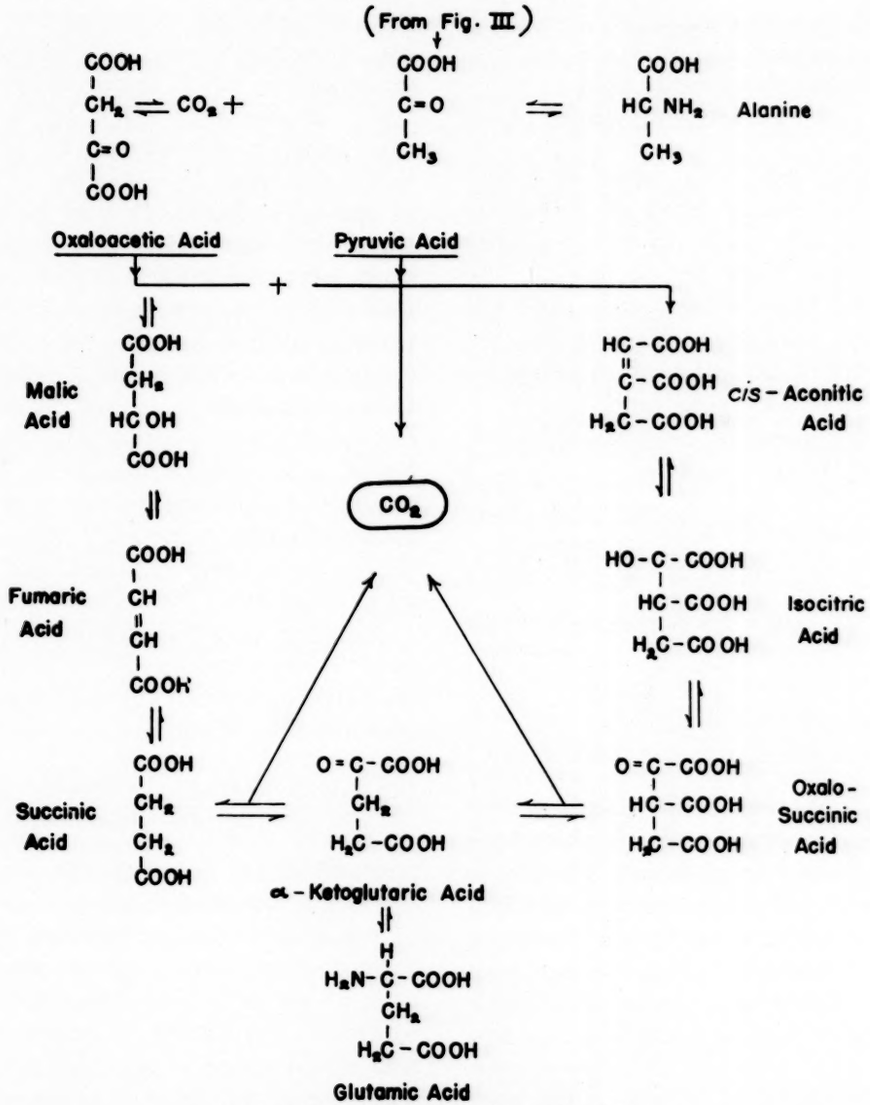


FIG. 4. The oxidation of pyruvic acid.

(15) fructose-1,6-diphosphate $\overset{\text{zymohexase}}{\rightleftharpoons}$ glyceraldehyde-3-phosphate + dihydroxyacetone phosphate.

These two isomeric compounds form an equilibrium mixture in that they are biologically interconvertible:

(16) dihydroxyacetone phosphate $\overset{\text{triose isomerase}}{\rightleftharpoons}$ glyceraldehyde-3-phosphate.

Glyceraldehyde-3-phosphate next undergoes spontaneous reaction with inorganic phosphate to yield glyceraldehyde-1,3-diphosphate. It should be noted that the phosphate bond thus established is of the low energy variety (table). When this compound is oxidized by the transfer of hydrogen to coenzyme I:

(17) glyceraldehyde-1,3-diphosphate + coenzyme 1 (ox.) $\rightleftarrows$ 1,3-diphosphoglyceric acid + coenzyme 1 (red.),

the phosphate in position 1 is transformed from a low energy phosphoric acid acetal into a high energy mixed anhydride of phosphoric acid (table), capable of delivery to other high energy systems:

(18) 1,3-diphosphoglyceric acid
+ adenosine diphosphate
⇄ 3-phosphoglyceric acid
+ adenosine triphosphate

The last three reactions have in effect augmented the energy level of inorganic phosphate, initially zero, up to an energy level sufficiently high to permit of the regeneration of high energy adenosine triphosphate, the energy in this case derived from the energy of oxidation of an aldehyde up to the level of a carboxy acid.

The rearrangement of 3-phosphoglyceric acid according to the reaction:

(19) 3-phosphoglyceric acid $\xrightleftharpoons{\text{triose mutase}}$ 2-phosphoglyceric acid,

is followed by the dehydration of this product:

(20) 2-phosphoglyceric acid $\xrightleftharpoons{\text{enolase}}$ phospho (enol) pyruvic acid + H_2O

In this reaction once again one sees the augmentation of energy level in a phosphate bond. In the starting material, phosphate occurs as an ester of a secondary alcohol, at low energy level, whereas in the product, phosphate is present as a high energy enol ester (table). The regeneration of another mol of adenosine triphosphate is thus made possible, at the expense of the energy yielded by glycolysis, as is seen in the next reaction of the series:

(21) phosphopyruvic acid
+ adenosine diphosphate ⇄ pyruvic acid
+ adenosine triphosphate.

The possible fates of pyruvic acid (Fig. 4) which, in alkaline solution, exists as an equilibrium mixture of the enol and keto forms, are several.[7] Under conditions of oxygen lack, when the several coenzymes of the hydrogen transport system are largely in the reduced state, the reaction:

(22) pyruvic acid + coenzyme I (red.)
⇄ lactic acid + coenzyme I (ox.)

may be expected to proceed to the right to an appreciable extent, and in these circumstances, since lactic acid appears to have no pathway open to it other than excretion or reoxidation to pyruvic acid, lactic acid may be expected to accumulate in the body fluids. It may be pointed out that lactic acid ($C_3H_6O_3$) is grossly at the same level of oxidation as glucose ($C_6H_{12}O_6$) and that in the reactions described thus far, there is neither an over-all consumption of oxygen nor a liberation of carbon dioxide. In fact all these reactions do run, in many circumstances, completely anærobically, lactic acid accumulating as glucose disappears. In general, however, when oxygen is abundantly supplied, pyruvic acid is drained into other channels and the equilibrium of reaction 22 is shifted to the left.

Another possible disposition of pyruvic acid is its conversion to alanine by the transfer of an amino group from some other amino acid:

(23) pyruvic acid + glutamic acid $\xrightleftharpoons{\text{transaminase}}$ alanine + α-ketoglutaric acid,

a reaction for which pyridoxal phosphate has been shown to serve as a coenzyme.

Yet another fate of pyruvic acid is today supposed to entail a preliminary degradation to an as yet unidentified two-carbon fragment, sometimes referred to as "acetyl," and condensation of this product with oxaloacetic acid to yield *cis*-aconitic acid. In order to balance the over-all reaction:

(24) Pyruvic acid + oxaloacetic acid
+ $\frac{1}{2}O_2$ → *cis*-aconitic acid + H_2O
+ CO_2,

it will be noted that oxygen is required among the reactants and carbon dioxide occurs among the products. This reaction, which initiates the so-called "tricarboxylic acid cycle," may be taken as the first individual reaction which is necessarily aerobic. A coenzyme necessary for this, and indeed several other reactions of pyruvic acid, is thiamine pyrophosphate, and the increase in blood and urine pyruvate levels

in thiamine deficient states has been ascribed to inhibition of this reaction. It is noteworthy that the other reagent required for this disposition of pyruvic acid, oxaloacetic acid, may in turn arise from pyruvic acid:

(25) pyruvic acid + CO_2 $\rightleftarrows$ oxaloacetic acid.

The hydration of *cis*-aconitate:

(26) *cis*-aconitic acid + H_2O $\rightleftarrows$ *iso*-citric acid

is followed by its dehydrogenation:

(27) *iso*-citric acid + $\frac{1}{2}O_2$ $\rightleftarrows$ oxalosuccinic acid + H_2O,

and here again, to balance the over-all reaction, oxygen is required. Oxalosuccinic acid now undergoes decarboxylation:

(28) oxalosuccinic acid $\rightleftarrows$ α-ketoglutaric acid + CO_2,

eliminating a second mol of carbon dioxide. The α-ketoglutaric acid thus formed may, by acceptance of an amino group, be transformed into glutamic acid. It may, on the other hand, undergo oxidative decarboxylation:

(29) α-ketoglutaric acid + $\frac{1}{2}O_2$ $\rightleftarrows$ succinic acid + CO_2

Three mols of carbon dioxide have now been eliminated, corresponding to the three carbon atoms of the pyruvic acid with which this, the aerobic phase, was initiated. The remaining reactions of the cycle, now called the "dicarboxylic acid cycle," may be pictured as serving to regenerate, from succinic acid, oxaloacetic acid:

(30) succinic acid + $\frac{1}{2}O_2$ $\rightleftarrows$ fumaric acid + H_2O;
(31) fumaric acid + H_2O $\rightleftarrows$ malic acid;
(32) malic acid + $\frac{1}{2}O_2$ $\rightleftarrows$ oxaloacetic acid + H_2O.

Oxaloacetic acid is thus conserved and may react with another molecule of pyruvic acid in a cyclic fashion. It may, in addition, accept an amino group to yield aspartic acid. Three of the keto acids which arise in the course of glucose catabolism, pyruvic, α-ketoglutaric and oxaloacetic, may readily and reversibly be converted into amino acids, and, in this fashion, a fusion of the metabolic pathways of proteins and carbohydrates is effected. At some point as yet undefined in the series below pyruvic acid, probably at the level of the two-carbon "acetyl fragment," a similar fusion of pathways of carbohydrate and fatty acid metabolism occurs whereby the over-all conversion of glucose to fatty acid takes place, on the one hand, and the products of fatty acid degradation feed into the tricarboxylic acid cycle, on the other.

Perhaps the most striking fact about this series of reactions is the occurrence of numerous individual steps whereby energy is released in small packages, rather than all at once in an explosive fashion. This gradual release of energy permits of its more efficient utilization in the endergonic processes of the body, and certain of the energy links that occur as glucose is degraded to pyruvate have been described. It should be pointed out, however, that the yield in energy as glucose is converted to pyruvate is far less than the yield obtained when pyruvate is further degraded to carbon dioxide, and of the energy links operating in this, the oxidative phase, little is known.

MAINTENANCE OF BLOOD GLUCOSE

For the cells of the body to carry out these reactions on glucose, a certain minimum concentration of glucose in the extracellular fluid must be maintained. One of the important mechanisms operating in this direction is the kidney, which normally prevents the loss of significant quantities of glucose in the urine as long as the level of blood glucose is below the threshold value. This is accomplished by the more or less quantitative reabsorption of glucose from the glomerular filtrate, a process in which the tubule cells transport at least a portion of the glucose against a concentration gradient. Such transport cannot be ac-

counted for on the basis of simple diffusion and necessarily consumes energy, and in view of the fact that such "up-hill" transport of glucose operates not only at the renal tubule but also at the intestinal mucosa and possibly elsewhere, it may be well to consider whence the necessary energy may arise. The sequence of events may be pictured as follows: Glucose diffuses across the barrier separating the lumen from the contents of the tubule cell; once in the cell it is phosphorylated according to reaction 11, which, in effect, disturbs the equilibrium in favor of diffusion of glucose into the cell from the lumen. Whereas glucose-6-phosphate does not escape from the cell, it may be pictured as circulating in the cytoplasm of the cell and coming in contact with a phosphatase which effects an irreversible hydrolysis according to reaction 8. A high concentration of glucose may thus be built up locally, and glucose may then diffuse from the intracellular fluid into the blood stream. To compute the energy which would be expended by such a sequence of events, one has merely to add reactions 8 and 11, the sum being:

(33) adenosine triphosphate
→ adenosine diphosphate
+ inorganic phosphate.

In other words, to transport one molecule of glucose against a concentration gradient by this means entails the loss of one high energy phosphate bond. That some such mechanism is operating at the renal tubule is indicated by the fact that phlorhizin, a known poison of phosphorylating systems, decidedly inhibits the tubular reabsorption of glucose.

Factors other than renal activity which serve to maintain the blood glucose at normal levels may conveniently be considered with reference to the endocrines which control these factors. Thus, the effect of epinephrine on carbohydrate metabolism may be assigned to an enhancement of the conversion of glycogen to glucose-6-phosphate (reactions 9 and 10). In the well nourished animal, with ample hepatic glycogen, the major effect observed is a decrease in the quantity of glycogen of the liver and an increase in the quantity of blood glucose, arising from the ready hydrolysis of glucose-6-phosphate in the liver (reaction 8). In the previously fasted animal, however, in which the glycogen of the liver is depleted, the injection of epinephrine is followed by a decrease in glycogen of the muscle. At this site, however, glucose-6-phosphate cannot be hydrolyzed, and the glucose-6-phosphate therefore follows the path of anaerobic glycolysis (reactions 12 through 22) and the resulting lactic acid escapes into the bloodstream. The depleted liver captures a fraction of this lactic acid, which it may then convert into glycogen.

The anterior pituitary gland produces a specific inhibitor of the enzyme hexokinase (reaction 11).[8] It appears to operate predominantly on the hexokinase of muscle and liver cells, and has little or no effect on the hexokinase contained in the cells of the central nervous system, the renal tubule or the intestinal mucosa. Since the hexokinase-catalyzed phosphorylation of glucose is, in a sense, a key reaction in the utilization of glucose, the presence of an excess of this inhibitor would be expected to interfere with the utilization of glucose, especially in muscle and in liver. A retardation in the formation of glucose-6-phosphate at these sites will result in an impairment of the utilization of glucose by these tissues as well as a decrease in the formation of all the substances which these tissues normally generate from glucose, among others, lactic and pyruvic acids, glycogen, fatty acids and carbon dioxide.

One of the actions of the secretion of the adrenal cortex appears to be an enhancement and prolongation of the action of this pituitary hexokinase inhibitor. When present in excess, essentially the same effects on the utilization of glucose by muscle and liver may be anticipated. The oxygenated steroids of the adrenal cortex are believed to have another effect on carbohydrate metabolism, namely, they are supposed to

favor gluconeogenesis at the expense of glucogenic amino acids of the proteins of the body. Both of these actions of the adrenal cortex will operate to increase the level of blood glucose, the one by impeding utilization and the other by favoring glucose synthesis.

An important action of insulin lies in its antagonism to the action of the inhibitor of hexokinase. Whereas insulin has no effect on hexokinase itself, it does serve to release this enzyme from the inhibition imposed on it by the anterior pituitary and the adrenal cortex. Assuming hexokinase in the normal animal to be continuously moderately inhibited, the action of insulin would be to remove this inhibition and, thus, indirectly to stimulate the enzyme. The phosphorylation of glucose would then proceed more rapidly, glucose would disappear from the extracellular compartment, glucose-6-phosphate would be formed in abundance in muscle and liver cells, and products derived from glucose-6-phosphate would secondarily be formed at greater than normal rates. Essentially all of these effects have been observed to follow the administration of insulin. Insulin lack, on the other hand, would be expected to simulate, chemically, the picture described as following the presence of an excess of hexokinase inhibitor. This picture is, in fact, a good description of the biochemical defect in diabetes mellitus.[9]

The release of insulin by the cells of the islets of Langerhans appears itself to be dependent on the level of blood glucose; the higher the blood glucose, the more insulin discharged. This mechanism is subject to exhaustion, however, and prolonged maintenance of the blood glucose at an excessively high level is followed, in certain species, by irreversible injury to the islets and the picture of permanent diabetes.[10]

In the adult normal animal in balance and at constant weight, the glucose made available by the various processes that have been described must be equal to the glucose that is being consumed in the several processes outlined. The magnitudes of these several processes in human beings have not been exhaustively studied. In the rat it would appear that about one third of the glucose is used in the elaboration of fatty acids which are needed to replenish the fat stores of the body, and only about one thirtieth is required for the maintenance of the glycogen reserves. The remainder is presumed to be degraded ultimately to carbon dioxide and to contribute carbon atoms along the way to other compounds which the body may synthesize from such fragments.

There is no specific nutritional deficiency related to the lack of glucose in the diet. However, it has long been recognized that when, for any reason, the rate of utilization of glucose is subnormal, there is a likelihood of the development of ketonemia and ketonuria. This may arise as a result of deprivation of dietary glucose, diabetes or renal glucosuria and may in general be rectified by the reestablishment, by suitable procedures, of normal glucose catabolism. This action of glucose, its so-called "antiketogenic" action, is today fairly well understood. The ketone bodies are not abnormal metabolites, but are formed normally and abundantly in the course of fatty acid degradation, probably chiefly in the liver. They do not accumulate in the blood of the normal person because they are normally consumed in muscle and liver as rapidly as they are formed. Only when they are produced in excessively large amounts do clinical ketonemia and ketonuria develop, and this is undoubtedly what happens when, for one reason or another, glucose is not being utilized at the proper rate. When glucose is scarce, either because of lack of dietary carbohydrate or because of loss of glucose in the urine, or when glucose, though abundantly present, is not being catabolized at a normal rate, excessive quantities of fat are transported from the depots to the liver and there degraded, probably to two-carbon "acetyl" fragments, and a portion of these are converted into acetoacetic acid. If these normal processes

become sufficiently exaggerated, the rate of acetoacetic acid formation will exceed the body's capacity to destroy this compound and its level in the blood will rise. The reestablishment of carbohydrate metabolism in such a subject appears to relieve the liver of the necessity of degrading fatty acids at excessive rates, and as the formation of ketone bodies resumes its normal rate, the ketone bodies which had accumulated in the body are either excreted in the urine or destroyed by the tissues of the body in their normal fashion. It may be noted in passing that acetoacetic acid and "acetyl," with which it is interconvertible, are believed to be catabolized by initial condensation with oxaloacetic acid to yield the same *cis*-aconitic acid encountered in the breakdown of glucose (reaction 24). From this point on the breakdown of acetyl, derived from fatty acids, and of pyruvate, derived from glucose, apparently follow identical pathways.

FUSION OF METABOLIC PROCESSES

From the foregoing discussion it will be apparent that the catabolic pathways of the carbohydrates, fats and proteins cross at many points and that within wide limits one nutrient may be substituted for another without significant injury to the metabolizing tissue. Each of the three major classes of nutrients may supply organic fragments which feed into the tricarboxylic acid cycle, a sequence of reactions which apparently serves to supply a large portion of the energy need of many biologic systems. As this fusion of metabolic pathways has been elucidated, the classic lines of demarcation between the metabolisms of fat, protein and carbohydrate have become progressively more obscure and more meaningless. The picture that is developing is one of reaction sequences, often cyclic, which liberate energy as needed by the organism, and these cycles apparently may be fed at many points and in many ways. Although extreme deviation from the normal composition of the nutrient mixture may result in the undue accumulation of one or another intermediate, a considerable degree of variation is tolerated. Whereas the catabolic breakdown of protein, fat and carbohydrate will undoubtedly continue to be taught, for purposes of convenience, as separate entities, the better understanding of these processes is leading to a more highly integrated point of view.

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Studies in Experimental Diabetes*

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SINCE Minkowski and von Mering in 1889 first discovered that removal of the pancreas in dogs led to the development of diabetes,[1] much attention has been given to the study of this disease in experimental animals. Depancreatized dogs show the signs and symptoms of diabetes and usually will die in less than three weeks if untreated. They exhibit not only profound changes in the metabolism of carbohydrate but also in the metabolism of protein, as indicated by the increased nitrogen excretion and of fat, as evidenced by excessive ketone body formation; changes abnormal in quantity rather than in kind. The experiments in which the pancreas was removed indicated that normally something was provided by the pancreas which was necessary to prevent the occurrence of diabetes. This was supported by the finding that if a piece of the pancreas was transplanted to another part of the body, diabetes was prevented.[2] The hormone nature of this pancreatic factor seems obvious now but it was by no means settled until insulin was discovered. It was not until 1922 that a potent, non-toxic extract of pancreas was prepared by Dr. F. G. Banting and Dr. C. H. Best at the University of Toronto.[3] By the use of this extract they were able to alleviate the diabetes of depancreatized dogs and later of hospital patients.

The effect of insulin in the diabetic is to relieve the diabetes. However, insulin does not entirely substitute for the removal of the pancreas since the other pancreatic secretions are lacking as well. Depancreatized animals require raw pancreas, lecithin or choline in addition to the insulin or their livers become large and fatty.[4] Observations made during the study of experimental diabetes resulted in the discovery of lipotropic factors and the opening of a new field of medical research.

Insulin is produced in the pancreas and there is, as yet, no evidence for any truly extrapancreatic source. It is secreted by the islets of Langerhans, the beta cells of which seem to be the essential endocrine structures. Their importance is indicated by a great deal of evidence not the least of which is the fact that the insulin content of the pancreas under different experimental conditions is closely related to the degree of granulation of the beta cells as shown by the neutral ethyl violet-Biebrich scarlet stain of Bowie.[5] This stain seems to be superior to most of the special islet stains for demonstrating the changes in granulation of the beta cells although it seems inferior to some in differentiating between the different types of cell in the islet. Using Bowie's stain, when the granulation of the beta cells is reduced, the insulin concentration in the pancreas is diminished also.

It would appear from what has been said that diabetes results from a deficiency of a particular hormone, insulin, manufactured by the beta cells of the pancreatic islets. In fact, we may define diabetes as a chronic metabolic disease which results from a relatively insufficient supply of insulin by the beta cells of the islets of Langerhans. This relative lack may result from a *reduced* insulin *supply* or it may result from a greatly *increased* insulin *need*.

For a while it seemed that the pancreas alone was involved in diabetes but later it appeared that other organs were also implicated. A number of findings led to this

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conclusion. First there was the evidence that in some animal species removal of the pancreas did not lead to the development of a severe diabetes but only to a very mild form of the disease. This suggested that some extra-pancreatic factors must be included in any consideration of the diabetic state. The liver is one organ known to be necessary for the production of diabetes since after removal of the liver the blood sugar falls even in depancreatized animals.[6] It has been shown, too, that certain endocrine glands other than the pancreas are involved. Houssay and Biasotti in 1930[7] found that the diabetes resulting from pancreatectomy could be alleviated by removal of the pituitary gland. It was shown by these and other workers that extracts of the anterior pituitary gland would bring back the diabetes once more, and that even in normal intact dogs injections of the extracts gave rise to a diabetic state. Diabetes may be alleviated also by removal of the adrenal glands[8] and, to a less extent, by removal of the thyroid gland.[9]

As a result of these experiments, it can no longer be said that the absence of beta cells of the islets is responsible entirely for the diabetic picture. It would appear that the presence of the pituitary and certain other endocrine glands is essential, too. There are then two antagonistic systems, one necessary to prevent diabetes and one tending to cause diabetes. When the one tending to cause diabetes predominates, diabetes results.

It will be evident from what has been said that there are many problems remaining in the study of diabetes. These can best be studied in the experimental animal in which conditions may be more or less controlled. Let us look for a moment at the ways in which diabetes can be produced experimentally. It was noted earlier that diabetes can be produced by pancreatectomy. It can be produced, too, by removing almost but not all the pancreas, i.e., by extensive *partial* pancreatectomy. Such a partially depancreatized animal is useful because the changes in the islets of Langerhans in the remnant of pancreas can be followed. The characteristic changes in the islets found in these diabetic animals are degranulation and hydropic degeneration of the beta cells.[10,11]

The third method of producing diabetes experimentally is by the injection of extracts of the anterior pituitary gland mentioned briefly before.[12,13] It should be pointed out that there is a great species difference in the response to these pituitary extracts. Diabetes can be obtained in the intact adult dog or cat by their injection but not in the young of these species nor in the rat, which is very resistant. In the adult dog pituitary diabetes can be separated into two phases, a transient diabetes present during the injections of the extracts and a permanent diabetes which is to be observed, under some circumstances, after the injections of pituitary extracts are stopped.

The diabetes that occurs while the extracts are being injected is known to require the presence of the liver[14] and, according to some, the adrenal glands also.[8,15] The diabetes resulting from the injection of the extract may be severe, with high fasting blood sugar values, glucosuria, increased ketone body formation and excretion, increased N excretion and other changes characteristic of diabetes. If the extract has not been too potent or the injections too prolonged, the diabetes stops shortly after the injections are discontinued. However, if the effect of the extract is great enough, the diabetes persists after the injections are discontinued, that is, it becomes permanent.

During the course of injections of the anterior pituitary extract certain changes take place in the pancreas. The insulin content of the pancreas is greatly reduced (to less than $\frac{1}{10}$ of the normal value) and there are extensive changes in the islets of Langerhans.[16,17] The beta cells show progressive degranulation and finally hydropic degenerative changes. If the effect of the injections is not too great, after they are discontinued the islet cells can be restored and the insulin content of the pancreas comes back to normal levels. If the extract

is more potent or the length of administration greater, the islets may be permanently damaged and a permanent reduction in normally functioning beta cells and a permanent lowering of the insulin content of the pancreas result. The persistence of the diabetic state after the anterior pituitary extract is stopped is dependent, therefore, on a permanent reduction in islet tissue; in effect, a removal of the beta cells instead of a removal of the pancreas as a whole. When the anterior pituitary injections are first given, the diabetes is fundamentally a pituitary diabetes (hypophyseal diabetes). Later, the persistence of the diabetic state depends on pancreatic changes and the diabetes is fundamentally pancreatic (metahypophyseal diabetes).

F. G. Young, who first studied metahypophyseal diabetes extensively, has reported recently that in cats a pituitary-induced diabetes may disappear despite the persistence of hydropic degenerative changes in the beta cells of the islets.[18] This observation has not yet been explained. While suppression of endogenous pituitary activity would seem to be the simplest postulated cause, Young states that there is no histologic evidence for this.

It is not possible to discuss here the nature of the diabetogenic pituitary factor. Long and Lukens reported that after removal of the adrenals the diabetogenic effect of pituitary extracts was not observed. This suggests that something acting through the adrenals may be involved. Young believes, however, that the diabetogenic effect of pituitary extracts is not due to an adrenocorticotrophic material (ACTH) since his diabetogenic pituitary preparations produced no obvious response in human patients whereas ACTH has been reported to produce a diabetic state in man. The evidence is increasing that purified growth hormone, as well as adrenocorticotrophic hormone, is diabetogenic in some species.

The importance of the adrenal glands in the genesis of diabetes has been shown by the fact that removal of the adrenals ameliorates to some extent the diabetes resulting from pancreatectomy. Adrenal cortical substances themselves will cause hyperglycemia and glycosuria when administered in sufficient quantities to normal rats[19] but these changes disappear when the injections cease and no permanent diabetes results. Similar effects have been obtained with pituitary adrenocorticotrophic material (ACTH) in rats,[20] and a temporary diabetes resistant to insulin has been induced in man by the administration of purified preparations of ACTH.[21] A reduced tubular absorption of glucose contributed to the glycosuria in these patients. There was at the same time a decreased concentration of blood glutathione and an increased excretion of uric acid in the urine. These changes are interesting in view of the fact that Griffith[22] has reported the production of diabetes in the rabbit by the administration of uric acid in the presence of lowered blood levels of glutathione (see alloxan). The administration of glutathione to subjects showing hyperglycemia and glycosuria as a result of the injections of ACTH caused these changes to be reversed.[23]

What has just been discussed constitutes the fourth method by which diabetes may be produced experimentally, namely, by the administration of adrenal cortical substances or by the injection of purified pituitary adrenocorticotrophic materials.

A fifth and lesser diabetogenic effect is that produced by estrogens. Despite the reported fact that estrogens may reduce the amount of insulin which the diabetic patient requires, these materials are diabetogenic in rats whose caloric intake has been maintained by force-feeding. The way in which this effect is brought about is not clear but it is apparently not mediated by the pituitary or adrenal glands.[24]

Thyroid administration should be included as the sixth way of producing diabetes though this effect has been obtained only when a large part of the pancreas has been removed.[25] Thyroid treatment in partially depancreatized diabetic rats, however, caused the diabetic state to disappear.[26]

The seventh way of producing a permanent diabetes experimentally is by the injection of glucose. Dr. Lukens and Dr. Dohan of Philadelphia showed that repeated intraperitoneal injections of glucose in the cat led to degenerative changes in the islets of Langerhans and to a permanent diabetic state.[27]

It should be pointed out that the degenerative changes in the islets of Langerhans are much the same in the animals made diabetic by partial pancreatectomy, pituitary injections or glucose injections. In dogs the change is degranulation, hydropic degeneration and finally disappearance of the damaged beta cells, whereas in cats persisting hydropic beta cells are evident. There is good reason to believe that in all these cases the permanent islet changes result from exhaustion of the islet cells through overwork.

The last way of producing diabetes experimentally is by the administration of alloxan, an oxidation product of uric acid.[28] The islet changes following alloxan administration differ from those just mentioned. Here there is a specific necrosis of the beta cells, evident in a few hours and followed by the disappearance of beta cells in a few days. These cells apparently disappear without signs of inflammatory reaction. Alpha cells replace beta cells or agranular cells are evident. The insulin content of the pancreas is reduced.[29]

Doses of alloxan too small to produce diabetes may yet produce some changes in islet function. Subdiabetogenic doses of alloxan have been shown to lead to an impaired tolerance for glucose and to cause an enhanced diabetogenic effect of pituitary extracts in rats.[30]

Although the type of islet change is different in the alloxan-treated animals (a toxic necrosis rather than hydropic degeneration), the end result is the same, namely, the reduction in functioning beta cells of the islets of Langerhans. With the exception of the alloxan diabetic animals and others in this class, there is good reason to believe that the degenerative islet changes all result from overfunction of the beta islet cells.

In experimental diabetes the permanence of the state in all instances depends upon some permanent reduction in normally functioning beta cells of the islets of Langerhans. This, coupled with the fact that all types of experimental diabetes can be relieved by insulin, makes it seem possible that diabetes could be cured by sufficiently increasing the amount of insulin-producing tissue in the animal's pancreas. Since this may be so and also since several types of experimental diabetes are produced by exhaustive overwork of the beta cells, it seems important to find out what factors influence the growth of the islets and affect the elaboration and secretion of insulin.

This has been studied by measuring the total volume or weight of the islets and determining the insulin content of the pancreas. It should be pointed out that the insulin content of the pancreas represents a balance between the production of insulin and its liberation or secretion. It may in some instances also bear a relation to the total volume of the insulin-secreting tissue. In itself the insulin content of pancreas may give little information concerning islet function. It may be reduced, for example, by decreased production of insulin or by increased liberation of insulin. However, if the changes in the insulin content of pancreatic tissue are observed under a variety of conditions and other findings are correlated with these, the insulin values become more significant. Two examples will be given:

The first example concerns the effect of partial removal of the pancreas on the insulin content of the pancreatic remnant in the dog.[31] It is found that if a large but not excessive amount of the pancreas is removed (e.g., $\frac{4}{5}$), the animal does not become diabetic and the insulin content of the pancreas remains within the normal range. Since only one-fifth of the pancreas remains and is supplying sufficient insulin for the animal and yet the insulin concentration in the remnant is not reduced, it

follows that the production and liberation of insulin by the cells of the remnant over a period of time must be increased. The extent of the increase will be related to the amount of pancreas removed. When the amount removed is sufficient to result in diabetes, the insulin concentration in the pancreatic remnant is reduced to low values and the islet cells become hydropic. There seems to be some justification in concluding that the low insulin values and islet cell changes under these circumstances are due to overwork of the islet cells.

The second example concerns the effect of repeated insulin injections upon the insulin content of the pancreas.[32] When daily injections of adequate amounts of insulin are given to rats, the insulin content of the pancreas is reduced. Since insulin is being supplied by injection, it seems logical to conclude that the need for endogenous insulin is diminished and that the reduction in insulin content under these circumstances is not due to overactivity of the islets but rather to a *reduced* function of the islet cells. This is supported by the fact that the low insulin values are accompanied by the histologic finding of a lesser number of negative Golgi images in the beta cells of the islets of Langerhans, a finding usually taken to indicate reduced cellular activity. It should be noted, too, that the degree of beta cell granulation is decreased by the injection of insulin.

This brings up the point that a reduction in the specific granulation of the beta cells is related to the insulin concentration in the islet cells rather than to the state of activity of those cells. Hence it is important to recognize that a degranulated beta cell may be one with greatly increased activity or greatly reduced activity.

By comparison of the islet changes with those following partial pancreatectomy and by the use of insulin administration along with other given experimental procedures, it seems possible to conclude whether or not the given procedure itself produces its effect by increasing the activity of the islets or by reducing the activity of the islets. Taken in relation to other findings and under a variety of experimental conditions it does appear then that studies of the insulin content of pancreas may help to reveal the state of islet function.

The measurement of islet volume or weight is, at best, a tedious procedure but, in the rat, reliable data can be obtained reasonably quickly by the use of a vital staining procedure and a planimetric method of measurement.[33]

It is possible to relate some of the findings concerning islet volume and insulin content. It is found first of all that the volume or weight of the islets and the insulin content of the pancreas increase with age or body weight.[33,34] This seems to hold for humans as well as animals and the relation to body weight according to Ogilvie[35] obtains also in the obese human, fatty tissue apparently requiring no less insulin than other tissues. For the rat, within a wide weight range, the insulin concentration per Gm. of pure islet tissue is in the neighborhood of 100 to 200 units. This is the value one might expect in a tumor of pure islet tissue. In one islet tumor a value of 214 units per Gm. has been obtained.[36]

It has been found that, in general, those factors which reduce insulin production and liberation also reduce the growth of the islets in young rats, and those factors which lead to a stimulation of insulin secretion also increase the growth of the islets in young rats.

We can list the effects on the islets by saying that good examples of factors reducing islet activity and in young rats depressing islet growth are: (1) the repeated injection of insulin, (2) the reduction of the caloric intake and (3) the use of diets low in carbohydrate. Factors stimulating islet secretion and, in young rats, increasing islet growth are: (1) the injection of certain anterior pituitary extracts, (2) the administration of thyroid materials, (3) the use of a high carbohydrate diet and (4) the continuous injection or repeated injections of glucose.

Let us examine these effects briefly. Insulin administration in adequate doses in rats reduces the insulin content of the pancreas to less than half that of the control animals within seven days.[32] Such a short period of insulin administration gives no demonstrable reduction in islet volume, hence the change in the insulin content of the pancreas is due to a reduction in the concentration of insulin in the islet cells. When insulin is given to young growing rats for periods of from 20 to 160 days, however, a significant inhibition of the growth of the islets is obtained.[37] The total islet weights in the insulin-injected animals were less than in the control rats when compared on the basis of duration of the test or body weight. There is some evidence, too, though not very extensive, that when the insulin injections are discontinued the islet volume is restored to normal in a few weeks. There is as yet no good evidence that insulin administration alone ever reduces the islet tissue below the initial level.

Starvation or undernutrition are other factors exerting an important influence on the islets. Starvation greatly reduces the insulin content of the pancreas.[38] Yet starvation of equivalent severity, as judged by the percentage weight loss (17 to 30 per cent), gives no appreciable reduction in the islet volume.[33] Hence the reduction in the insulin content of the pancreas, as with short periods of insulin administration, is due to a reduction in the concentration of insulin in the islet cells. This is borne out by the finding of reduced granulation in the beta cells of the islets in the starved rats. The presence of few negative Golgi images in histologic sections suggests that the effect is related to a reduced activity of the islets, a suggestion that is supported by the finding that the insulin content of the pancreas and beta cell granulation are still further diminished if the fasted animals are injected with insulin.[32]

While over short periods, with complete starvation, a reduction in the islet volume was not observed, yet if young animals are undernourished for longer periods of time an influence on islet growth can be demonstrated.[37] When the intake of a balanced diet is just sufficient to maintain body weight but insufficient for growth, it is found after three to five weeks that the islets in the undernourished group have failed to grow, i.e., they do not show the normal increase in islet volume with age. The effects of fasting and undernutrition on islet growth and function are probably due to the restriction of carbohydrate intake. The insulin content of the pancreas is much less after a period on a diet very rich in fat than it is when an equicaloric amount of sugar is given.[38]

As a result of fasting or undernutrition marked changes in carbohydrate metabolism have been reported, grouped usually under the inclusive term "hunger diabetes." The response to the ingestion of carbohydrate is similar to that of the diabetic. There is hyperglycemia and glycosuria and a high, prolonged glucose tolerance curve. However, these animals differ from the diabetic in that successive doses of carbohydrate improve the condition. It is conceivable that the altered response to carbohydrate by the tissues of the starved animal results from a reduced continuous supply of insulin. Most studies, however, indicate that insulin administration increases the carbohydrate tolerance a little but does not restore it completely. The effect of a continuous injection of insulin should be tested.

Dr. Lundbaek, of Copenhagen, and Dr. Goranson, of Toronto, have shown that in the rat fasting, even for short periods of time, causes a definite increase in the phosphorylase activity of muscle.[39] This is due to an increase in the relative proportion of the active *a* form of phosphorylase as compared to the inactive *b* form. The *a* or active form of phosphorylase is thought to be converted to the inactive *b* form through the action of the P-R (prosthetic-group removing) enzyme. Hence an increase in phosphorylase *a* on fasting suggests that the action of this P-R enzyme has been diminished. The change in phosphorylase activity and presumably of the P-R enzyme is quickly reversed by refeeding the fasted animal. An

increase in phosphorylase activity on fasting probably assists in the mobilization of glycogen stores at a time when no exogenous carbohydrate is available.

It seems obvious that the effect of fasting on carbohydrate metabolism must be due to some alteration in the activity of those tissues which are important in the new production, storage, liberation or use of sugar. One of the important changes may be the increase in phosphorylase activity which has just been discussed.

Diet also affects the volume of the islets of Langerhans. It has been shown by Tjening that growing animals on a high fat diet for a long period of time have a smaller volume of islet tissue than those fed a high carbohydrate diet.[40] The various factors mentioned, insulin administration, fasting or undernutrition and high fat or low carbohydrate intake, appear to decrease the insulin content of pancreas and to diminish the growth of the islets in young rats as a compensation for a diminished need for endogenous insulin.

The factors stimulating islet activity are those which increase the need for insulin. Young and his associates showed that injections of crude saline extracts of the anterior pituitary gland lead to an increase in insulin content of pancreas[41] and to increased islet growth in young rats.[42] We have confirmed the effect on islet growth.[37] A positive correlation between islet size and the size of the pituitary has been reported by Tjening. While these facts point to a pituitary pancreatrophic effect, the evidence that the pituitary gland normally exerts any essential regulation of islet function is not at all convincing. Krischesky[43] reports an increase in islet tissue following hypophysectomy in the rat, although his published data could be interpreted as showing no significant change. In our studies it was found that hypophysectomy does not lead to any significant reduction in the insulin content of the pancreas or the islet volume below that of paired-fed control animals although the values obtained are considerably less than in control animals fed ad libitum.[37] Any effects that do occur in the hypophysectomized animals might be ascribed to undernutrition. Moreover, the insulin-lowering effect of fat-feeding can still be obtained after removal of the pituitary gland and, having been lowered, the insulin content can be restored again to normal in such an animal by feeding a balanced diet.[44] These findings would seem to indicate that the pituitary is not fundamentally involved in these changes. The pancreas seems able to regulate the production and liberation of insulin independently of the pituitary gland.

Administration of desiccated thyroid also is reported to lead to an increase in the insulin content of pancreas[45] and it has been found that there is also an increase in the total bulk of the islets.[37] The effect on islet volume could not be demonstrated satisfactorily until after forty days. This is interesting in view of the report by Houssay and associates that the diabetes of partially depancreatized rats disappears as a result of thyroid treatment.[26]

By far the most rapid effect on the growth of the islets, with the factors yet investigated, is obtained by the continuous injection of glucose. This had been reported by Woerner to cause an increase in islet volume in guinea pigs[46] but quantitative data were not available. It was found in the experiments at the University of Toronto that the continuous injection of glucose intravenously for seven to ten days caused a marked increase in the mass of islet tissue in growing rats.[37] In fact, the islet tissue was doubled in volume in this time. From this it would appear that in a normal, intact, growing rat the islet tissue is very labile and responds to stimulation by growth as well as secretion. Work done in order to find whether or not the effect is mediated by the pituitary gland has been inconclusive as yet.

There is evidence that the activity of islet cells is stimulated by conditions elevating the blood sugar level. Whether or not the elevated blood sugar acts as a direct stimulus for the islets or whether blood insulin level is involved cannot be decided

at present. The experiments of Anderson[47] on the isolated perfused pancreas support the view that blood sugar level is the important factor. The recent experiments reported by Milman and Russell[48] are interesting in this regard. They found that highly purified growth hormone when injected intraperitoneally into normal male rats caused a significant and prolonged reduction in blood sugar level. In alloxanized or partially depancreatized rats, however, the injection of this material caused a rise in the blood sugar values. It is possible that the differences in the effects might be due to changes in the response of tissues in the presence of adequate or small amounts of insulin. It would seem more probable, however, that the pituitary growth hormone produces hyperglycemic or contra-insulin effects, but in the presence of adequate islet tissue these lead to a sufficient secretion of insulin to cause hypoglycemia. Since the effect is very prolonged, it would suggest either that insulin secretion may be stimulated in the presence of a falling blood sugar level or that the insulin secreted by the pancreas has a very prolonged effect. The experiments lend support to the view that some factor other than blood sugar level, possibly blood insulin level, is important in the stimulation of the secretion of insulin by the islet cells. Another interesting experiment not supporting this view is that of Peterson[49] who injected glucose quickly into the heart in large doses and found that in fifteen minutes there was degranulation of the beta cells of the islets. This degranulation was not prevented by the injection of insulin along with the glucose.

Because a procedure leads to an increase in the islet tissue in the rat does not mean that such a procedure is good or bad as far as the prevention of diabetes is concerned. Growth, in these experiments, can be considered as an evidence of islet stimulation.

It will be apparent that the factors which we have cited as increasing the insulin content or islet volume in the rat, namely, the administration of pituitary extract, thyroid extract or large amounts of sugar, are all diabetogenic in the adult dog or cat, i.e., they help to produce diabetes in these animals. In the intact rat, diabetes probably does not occur either because the increase in functioning islet tissue is great enough or because these factors do not increase the need for insulin as greatly in the rat as in the dog. At all events the compensatory increase in the insulin producing structures and in insulin secretion is great enough to prevent the onset of diabetes.

We can conclude from these data that certain factors stimulate the islets and certain factors depress them. In experimental animals the stimulating factors may produce diabetes; but if there is a sufficient compensatory increase in islet tissue and insulin secretion, diabetes may not occur. There is a species difference in this response and it is important to discover the reason for this difference.

One further point should be mentioned and that is that those factors which reduce islet activity can prevent or at least reduce the damaging effects on the islets of other procedures which ordinarily stimulate the islets excessively.[50] Fasting, fat-feeding or insulin administration, for example, all tend to prevent the injurious effects of pituitary injections on the islets of dogs, and fasting or insulin administration prevents the islet changes in animals with extensive partial pancreatectomy. The observation of Houssay and Martinez[51] of an adverse effect of fat in 95 per cent depancreatized rats is difficult to reconcile with these findings and further clarification of the effect of fat is required.

We know then that there are certain factors which stimulate the islets and which when excessive, or under certain other conditions, may cause diabetes. It is apparent, too, that certain other factors depress islet activity and can prevent the excessive stimulation of the islet cells, hence can prevent most but not all forms of diabetes in experimental animals. The exception is the diabetes resulting from the administration of alloxan.

Much remains to be done in elucidating the cause of diabetes and in finding factors which influence islet growth. Perhaps human diabetes can be prevented or cured. Much experimental work must be done in the investigation of the complications of diabetes, especially the vascular, renal and ocular changes. Investigations in this field are just beginning. Another problem requiring clarification is the effect of removal of the pancreas in alloxan diabetes, pituitary diabetes and human diabetes. Some report a decrease in insulin requirements[52,53] and others no change.[54] When a decrease is found, this may conceivably be due to an altered absorption of food materials or possibly to the removal of some influence of a pancreatic hyperglycemic factor. Hence the physiologic significance of the hyperglycemic factor must be determined.

We have mentioned the ways in which diabetes can be produced experimentally and have intimated that in all instances the existence of diabetes could be ascribed to a relative lack of insulin. Yet we have given no indication of how insulin acts or what essential changes are occurring in the tissues of the diabetic. We cannot at this point enter into a discussion of the mode of action of insulin. Its essential action is probably on some of the enzyme systems involved in the intermediate metabolism of carbohydrate. Cori and associates reported that insulin exerts an influence on the hexokinase system which is responsible for the phosphorylation of glucose and the bringing of it into the metabolic chain in the tissue cells.[55] Others have postulated different sites of action for insulin. Recently support has been found for a more generalized influence, namely, an increase in the efficiency of the coupling between phosphorylation and oxidation.

Goranson[56] has observed that the aerobic phosphorylation of creatine during succinate or malate oxidation in heart muscle preparations from alloxan diabetic rats was significantly less than in the normal although no significant difference in oxygen uptake was noted. Insulin injected into the alloxanized rats prior to the test caused no appreciable change in the oxygen consumption of heart muscle preparations but restored the ability of the tissue to synthesize phosphocreatine. This and other evidence led him to the conclusion that insulin participates directly in reactions in the tricarboxylic acid cycle leading to a more efficient coupling between the processes of phosphorylation and oxidation. According to present concepts the synthesis of adenosine triphosphate and phosphocreatine represent the chief means whereby the potential energy of carbohydrate, and presumably of the breakdown products of fat and protein, too, is transferred to energy-utilizing systems. Hence the more efficient coupling between the processes of phosphorylation and oxidation brought about by insulin would lead to an increase in the efficiency with which the potential energy of carbohydrate is made available for such endergonic processes as the synthesis of glycogen and other cellular components. Data are accumulating concerning the mode of action of insulin and one can assume that before long some fundamental action will be established.

We are not satisfied, however, with the state of our knowledge concerning experimental diabetes. Let me end by quoting Oscar Minkowski,[57] the man who first depancreatized a dog, produced and recognized experimental diabetes. "It may be useful . . . to point out, which the discovery of insulin shows clearly, that scientific research which does not lead immediately to a practical end, sooner or later may have success in practice. Also it is not necessary to solve every problem regarding the elements of nature in order to serve mankind. It is sufficient to search for the laws by which they work in order to master them."

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Association of Diabetes Mellitus and Disorders of the Anterior Pituitary, Thyroid and Adrenal Cortex*

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In most instances the disturbed metabolism of human diabetes mellitus is explainable on the basis of deficiency of insulin. In remarkably few cases, either preceding or following establishment of the diabetic state, is there clear evidence of disturbance of function of other glands of internal secretion which are known to play an important role in carbohydrate metabolism. In the majority of cases of diabetes the function of the anterior pituitary, thyroid and adrenal cortex is normal by all clinically available methods of measurement.

Nevertheless, there is good evidence that hyperfunction of the anterior pituitary, thyroid or adrenal cortex may, in an occasional case, contribute to the development of diabetes in susceptible individuals, or may intensify diabetes which is already existing. By the same token, when hypofunction of these glands of internal secretion results from destructive lesions or surgical extirpation, existing diabetes may be ameliorated in varying degrees.

In some cases of tumors of the pituitary or adrenal cortex, or of hyperplasia of the adrenal cortex, diabetes occurs and is apparently due primarily to hyperfunction of the involved gland. In such instances the presence of other stigmas of hyperfunction of the gland in question usually serve to distinguish the associated diabetes from the commonly observed forms of the disease. Furthermore, in such cases all evidences of diabetes may disappear when and if normal function of the anterior pituitary or adrenal cortex is restored.

Evidences of diabetes may also be observed in cases of thyrotoxicosis and may disappear with the restoration of normal function of the thyroid. Many authors regard these as cases of latent diabetes which are brought to light by the metabolic stress of hyperthyroidism rather than as cases of diabetes resulting solely from hyperthyroidism.

Animal experimentation has gone far in elucidating the role of the anterior pituitary, thyroid and adrenal cortex in carbohydrate metabolism, particularly the disturbed carbohydrate metabolism of experimental diabetes. What has been learned in this field from the study of animals can occasionally be applied directly to the human being. It is our purpose to present a group of cases of diabetes mellitus from the records of the Mayo Clinic in which the development or behavior of the disease was modified by either hypofunction or hyperfunction of the anterior pituitary, thyroid or adrenal cortex, and to discuss briefly the physiologic principles involved.

ANTERIOR PITUITARY AND HUMAN DIABETES

Diabetes Mellitus Associated with Acromegaly and with Hypopituitarism. That the anterior lobe of the pituitary body has profound effects on carbohydrate metabolism has been shown in many ways experimentally. Diabetes in depancreatized animals is

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made milder by hypophysectomy, as was demonstrated by Houssay[1] in his classic experiments. The diabetes of the Houssay animal is intensified by the administration of extracts of the anterior pituitary. Furthermore, as shown by Young,[2] permanent diabetes can be induced in animals by the administration of extracts of the anterior lobe of the pituitary. These facts and other evidence would suggest that hyperfunctioning lesions of the anterior lobe of the pituitary in human beings might frequently be associated with diabetes. This is at least partially true in that a higher incidence of diabetes occurs among patients with acromegaly than would be expected by chance. However, all patients with comparable hyperfunctioning lesions of the anterior pituitary are not diabetic and it is possible that a fundamental deficiency of the islets of Langerhans must exist before a hyperactive lesion of the pituitary can produce diabetes. The diabetes in these cases usually is mild and relatively insensitive to insulin. When the lesion of the pituitary becomes inactive, either spontaneously or as a result of treatment, the diabetes may become milder or may, for all practical purposes, disappear. The following case illustrates some of these points.

CASE 1. A white woman, fifty-five years of age, was well until October, 1948, when she noted the gradual onset of fatigue, pruritus vulvae, polydypsia, polyuria, loss of weight and blurring of vision. Glycosuria and a concentration of blood sugar of 384 mg. per 100 cc. were discovered by her physician and a diabetic diet was prescribed. Insulin was not used. The diabetes on her admission to the clinic a few weeks later was uncontrolled.

The appearance of the patient at this time suggested acromegaly. Her hands and feet were large and she stated that the size of her glove had increased from 6½ to 9 and that her shoes had to be wider but no longer than formerly. These changes had developed gradually during the previous two years. On questioning she admitted that headaches in the frontal region were rather frequently present in the mornings on arising. Prognathism was not present. Roentgenograms of the skull showed evidence of an enlarged sella turcica owing to an intrasellar tumor with decompression into the sphenoid sinus. A roentgenogram of a hand showed evidence considered typical of acromegaly. The value for blood sugar was 370 mg. per 100 cc. Urinary excretion of 17-ketosteroids was 11.7 mg. in twenty-four hours. The concentration of phosphate in the plasma was 3.3 mg. per 100 cc. The basal metabolic rate was +20 per cent. Visual fields were normal as were the ocular fundi. Results of neurologic examination were negative.

Diagnoses of pituitary tumor with acromegaly and diabetes mellitus were made. The diabetes was brought under control with some difficulty, but in about five days the sugar in the urine was markedly reduced. A mixture of insulin containing 20 units of protamine zinc and 42 units of regular insulin was given each morning before breakfast. The diet consisted of 1,962 calories. Insulin reactions did not occur. A course of roentgen therapy was given for the tumor of the pituitary and the patient was permitted to return home and advised to continue use of the aforementioned dose of insulin and diet.

When the patient returned in five weeks for a second course of roentgen therapy, she told of a striking change in the diabetes. During the first two weeks at home she continued to need a total of 62 units of insulin daily. An increased amount of sugar appeared in the urine during an upper respiratory infection. After this, however, there was a rapid drop in the requirement for insulin. During the second visit it was found that 10 units of protamine zinc insulin daily kept her urine free of sugar. On fasting the concentration of blood sugar was 147 mg. per 100 cc. Her strength had increased and she felt well. The second course of roentgen therapy was given.

Again, after an interval of five weeks, the patient returned for a third course of roentgen therapy. At this time the dosage of insulin was 6 units of protamine zinc daily. The urine was consistently free of sugar.

She did well for the next two weeks and then symptoms of increased intracranial pressure developed rather rapidly with headaches, vomiting and finally unconsciousness. She was brought to the clinic and immediately hospitalized; a lumbar puncture was cautiously performed. This revealed a protein content of 110 mg. per 100 cc. and 18 lymphocytes and 21 polymorphonuclear cells per cubic milliliter. The most

probable diagnosis was meningeal irritation associated with rupture of the intrasellar tumor. Treatment was conservative and recovery occurred slowly. During the period of increased stress the fasting blood sugar varied from 130 to 168 mg. per 100 cc. Insulin was not required and there was no glycosuria. At the time of her dismissal she was not taking any insulin and was again feeling well. Visual fields still showed no encroachment. The basal metabolic rate was +16 per cent.

This patient had apparently had active acromegaly due to a tumor of the pituitary for about two years at the time diabetes developed. The diabetes was not mild but was rather insulin-insensitive. Roentgen ray treatment of the pituitary gland was followed in several weeks by a rapid decrease in the severity of the diabetes. It cannot be concluded with certainty that the amelioration of the diabetic state was due solely to a decrease in function of the pituitary as the same type of change in severity of diabetes is occasionally seen when the disease is first brought under control. However, the fact that treatment for acromegaly was followed by such a profound change in the diabetes is highly suggestive. That the diabetes was actually milder after the treatment of the pituitary is further indicated by the fact that the stress of the severe illness described did not produce, temporarily, a more severe diabetic condition than was present before.

Almy and Shorr[3] have recently described a case of diabetes mellitus made manifest by acromegaly which disappeared completely when hypofunction of the anterior pituitary appeared. An abstract of the case is given here because evidence for hypofunction of the pituitary is stronger than it is in our case.

A man, forty years of age, had had acromegaly for fourteen years and diabetes for five years. The diabetes was relatively insensitive to insulin in that 60 units of protamine zinc insulin did not reduce the amount of sugar in the urine. The glucose tolerance curve indicated the presence of diabetes. Acute mastoiditis and basilar meningitis developed and mastoidectomy was performed. Eighteen days later the urine was free of sugar and fasting blood sugar and glucose tolerance curves became normal. Five years later he was still free of diabetes. During this period the sella turcica became reduced in size and the basal metabolic rate dropped to −30 per cent. There was no evidence of adrenal insufficiency. The authors attributed the sudden disappearance of the diabetes to partial degeneration of the anterior pituitary with consequent reduction in the elaboration of the diabetogenic principle.

Neither of these cases describes the appearance of hypofunction of the anterior pituitary of a patient with true diabetes mellitus, that is, diabetes due solely to a deficiency of insulin. Such an occurrence must be exceedingly rare. A search of the records of the Mayo Clinic for the past fifteen years reveals no authenticated case. Theoretically such a patient should show amelioration of the diabetes, just as pancreatic diabetes in the experimental animal is ameliorated by hypophysectomy.

THYROID GLAND AND HUMAN DIABETES

Diabetes Mellitus and Hyperthyroidism. An excess of thyroid hormone in non-diabetic individuals may produce glucose tolerance curves resembling those of patients with mild diabetes mellitus. This is probably due in part to an increased rate of absorption of glucose from the gastrointestinal tract and perhaps in part to impairment of the capacity of the liver to store glucose as glycogen. When hyperthyroidism develops in a case of diabetes, the decreased sugar tolerance already existing is further depressed and the diabetes becomes more severe. It is also important to note that diabetes may first become manifest with the onset of hyperthyroidism. All symptoms may easily be attributed to the uncontrolled diabetes and the diagnosis of hyperthyroidism overlooked. Any new diabetic who continues to lose weight and complains of excessive fatigue and nervousness after control of the diabetes has been accomplished should be suspected of having hyperthyroidism. This is especially true if the diabetes proves to be unexpectedly

difficult to control. Some of these points are illustrated in the following case reports.

CASE II. A white male, thirty-four years of age, was first seen at the clinic in April, 1934. He gave a history of diabetes mellitus of seven years' duration. Control had been good on three doses of regular insulin daily averaging 20 units each, for most of the seven years. However, increasing difficulty had been experienced in his diabetic management during the two years prior to his admission to the clinic. During this period he had noted weakness, increased perspiration, nervousness and intermittent watery diarrhea. There were many periods of heavy glycosuria and many severe insulin reactions. He was hospitalized on admission to the clinic in an attempt to control the diabetes. He required up to 115 units of regular insulin daily in divided doses. Even with this amount of insulin he excreted large amounts of glucose. (Fig. 1.) On a diet containing 113 Gm. of carbohydrate he excreted 98 Gm. of glucose in one period of twenty-four hours and 63 Gm. in another. Reactions were still frequent. A diagnosis of exophthalmic goiter was made on the basis of the signs and symptoms. The basal metabolic rate was +18 per cent. He was given strong iodine solution (Lugol's solution), 10 drops three times a day. With partial control of the hyperthyroidism by the iodine, his requirement of insulin dropped to 60 units daily. A subtotal thyroidectomy was performed and 28 Gm. of tissue were removed. The pathologic diagnosis was parenchymatous hypertrophy. Partial control of the glycosuria was obtained the day after operation with 90 units of insulin. The next three days after operation his insulin requirement gradually rose so that on the fourth postoperative day he was given 150 units. After this there was a gradual decrease in the amount of insulin required to control the diabetes. Three weeks after operation the urine was free of sugar on 35 units of insulin in three doses daily. This was the smallest dose of insulin he had ever taken.

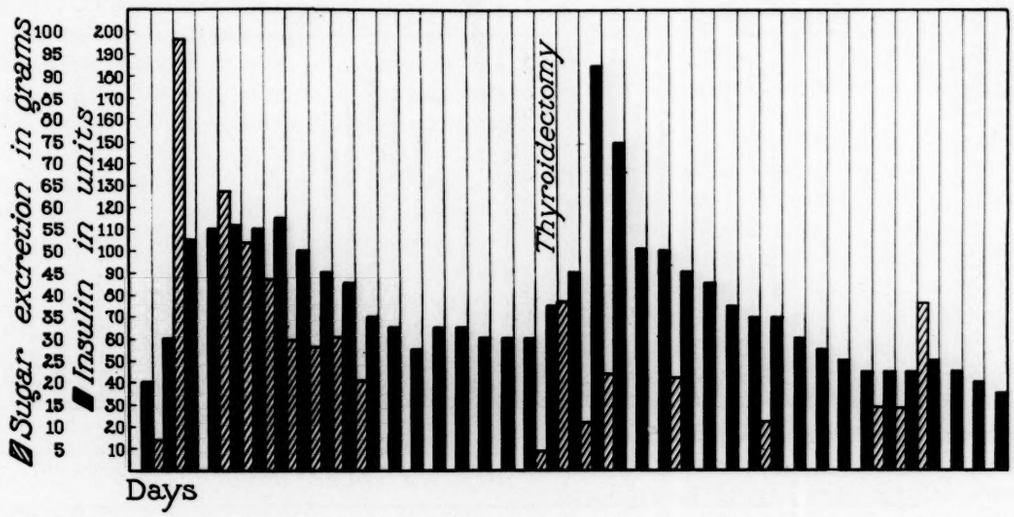


FIG. 1. The effect of thyroidectomy on excretion of glucose and requirement of insulin. (Case. II.)

CASE III. A white woman, forty-eight years of age, was first seen at the clinic in 1930. At this time a diagnosis of diabetes mellitus was made. Glycosuria was controlled on three doses of regular insulin a day. The total daily dosage was 40 units. During the next two years under her physician's care she was able to discontinue the use of insulin. She remained well until two months before her second admission to the clinic in 1933 at which time she began to experience weakness, palpitation, excessive perspiration, edema of the ankles and some loss of weight in spite of an excellent appetite. Shortly before her return to the clinic her blood sugar was found to be 300 mg. per 100 cc. Insulin was again employed and at the time of her admission she was taking 45 units daily in three doses. Nevertheless, she was still excreting moderate amounts of glucose in the urine. A diagnosis of exophthalmic goiter was made. The basal metabolic rate was +26 per cent. Administration of strong iodine solution, 10 drops three times a day, was started. Partial control of the hyperthyroidism was obtained but the insulin require-

ment increased until the day before operation, when 70 units were required. (Fig. 2.) After operation there was increased difficulty in controlling the diabetes. On the ninth post-operative day 155 units of insulin were given with only fair control of the glycosuria. The diabetes then became milder and by the time of her dismissal, twenty-seven days after operation, five units of regular insulin before breakfast and five units before supper sufficed to keep her urine free of sugar.

CASE IV. This case has previously been discussed by McDonough, Haines and Kepler.[4] A man, forty-three years of age, came to the clinic in 1939 complaining of loss of weight, ease of fatigue, weakness and intolerance of heat of six months' to one year's duration. In addition, for six months before admission polyuria and polydypsia had been present. A diagnosis of diabetes mellitus had been made and treatment with diet had been started. The patient also gave a history of thyroidectomy for exophthalmic

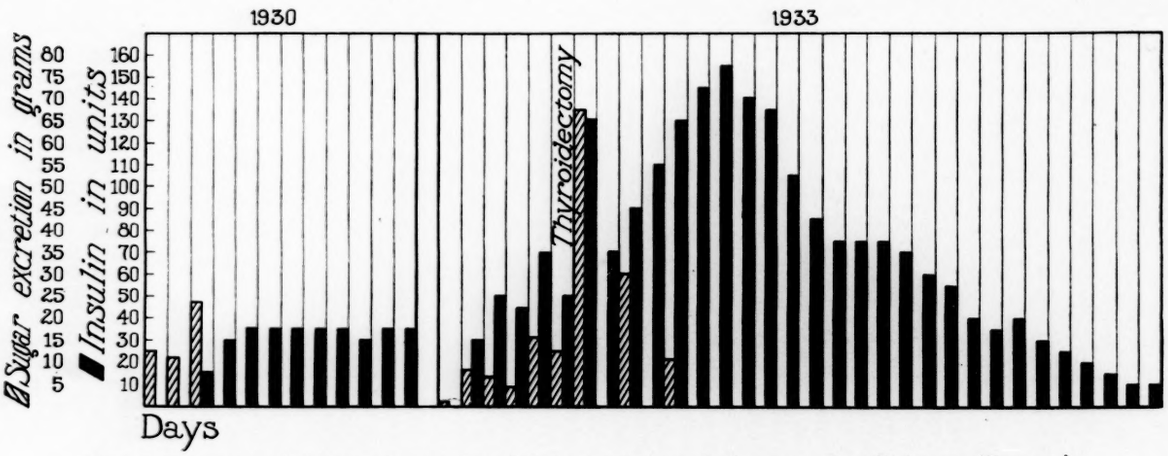


FIG. 2. The marked increase in severity of diabetes after surgical trauma is well shown. (Case III.)

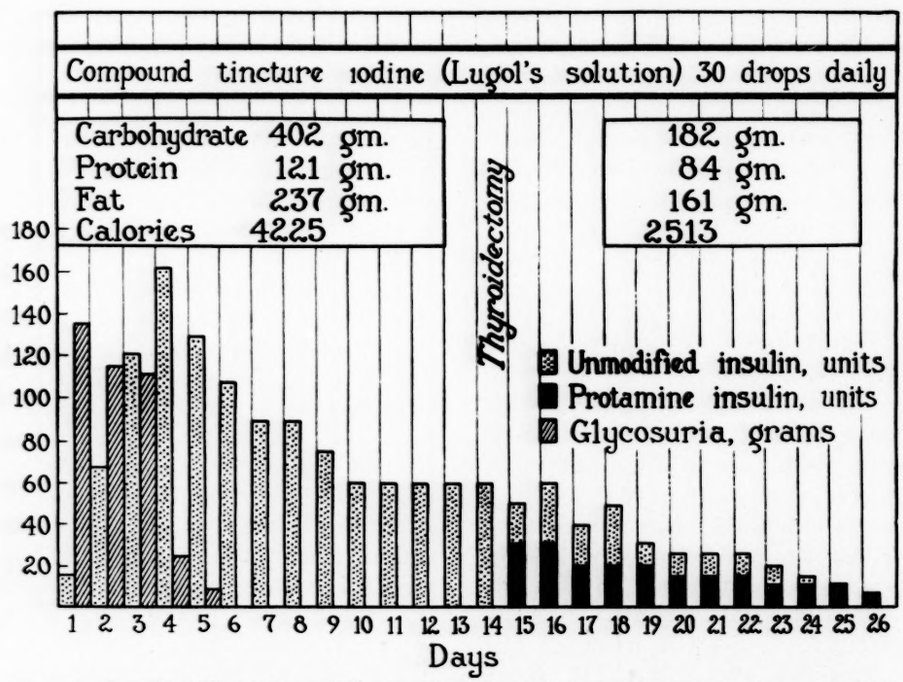


FIG. 3. Graphic illustration of the amelioration of the diabetic state by control of hyperthyroidism by the administration of strong iodine solution and thyroidectomy. (Case IV.) (From MCDONOUGH, F. E., HAINES, S. F. and KEPLER, E. J.[4])

goiter in 1935 with good relief of symptoms. At the time of his admission to the clinic the value of the blood sugar was 278 mg. per 100 cc. and his basal metabolic rate was +23 per cent. Diffuse enlargement of the thyroid was noted. Diagnoses of recurrent exophthalmic goiter and diabetes mellitus were made and the patient was hospitalized for treatment.

On the second day of hospitalization 160 units of regular insulin were required and only partial control of the glycosuria was obtained. As is shown in Figure 3, in spite of this large amount of insulin 110 Gm. of glucose was excreted in the urine. Strong iodine solution was administered and the basal metabolic rate dropped to +7 per cent and the amount of insulin required dropped to 60 units daily. Control of the diabetes continued to be good after operation and eleven days later only 10 units of protamine zinc insulin were needed for control of the glycosuria. One month after dismissal the patient was able to discontinue the taking of insulin entirely without the reappearance of sugar in his urine.

The patients in Cases II and III had had diabetes for some time before the onset of hyperthyroidism. In each case control of the diabetes had been relatively easy. However, with the metabolic stress of hyperthyroidism the diabetes became more severe. The patient in Case IV noted onset of the diabetes after hyperthyroidism had been present for some time. Partial control of the diabetes did not ameliorate the symptoms of fatigue and weakness. After operation all three patients showed a marked reduction in the amount of insulin required. In addition, the first two patients illustrate the increase in severity of diabetes which is usually seen for a short period after thyroidectomy when this combination of diseases is present.

Diabetes Mellitus and Myxedema. A decrease in thyroid function may produce effects on diabetic patients, the opposite of those seen with excess thyroid, that is, the diabetes may be ameliorated to some degree. However, the changes are not usually striking. Myxedema in non-diabetic persons may produce an increased tolerance to glucose administered orally. This effect is due in part to decreased rate of absorption from the gastrointestinal tract and, also, to decrease in general metabolism. Total lack of thyroid hormone would theoretically be helpful in controlling severe diabetes, and this has been attempted in at least one case (Case VI). Some of the effects of myxedema on human diabetes are illustrated in the following cases.

CASE V. A man, fifty-nine years of age, came to the clinic in July, 1941. His main symptoms were related to coronary sclerosis with rather frequent attacks of angina pectoris. Diabetes mellitus had been discovered two weeks previously. On physical examination it was found that the patient had a low-lying adenomatous goiter and persistent tachycardia. The basal metabolic rate was +20 per cent. The value for blood sugar was 242 mg. per 100 cc. The diabetes was brought under fair control by diet and a mixture of 6 units of protamine zinc insulin and 18 units of regular insulin daily before breakfast. He was given strong iodine solution, 10 drops three times daily, and sent home to return in a month for thyroidectomy. During this period the diabetes was under good control although he still needed 24 units of insulin mixture a day.

Upon his return to the clinic thyroidectomy was performed and the pathologic report was multiple adenomas in a gland showing parenchymatous hypertrophy. There was rather marked intensification of the diabetes the first few days after operation, and 140 units of insulin were required on the fourth postoperative day. The amount of insulin required dropped rapidly thereafter. When the patient was dismissed three weeks after operation, the basal metabolic rate was −21 per cent. There were no clinical signs of myxedema.

At home his insulin requirement continued to drop and two months after operation he was taking a mixture of only 6 units of protamine zinc and 4 units of regular insulin. With this dose he was having mild insulin reactions. The insulin was soon stopped altogether and he continued to be aglycosuric. In addition, rather frank signs of myxedema had developed. He returned to the clinic a few weeks later complaining of dry skin, sluggishness, fatigue and intolerance to cold. The basal metabolic rate was still −21 per cent. The concentration of cholesterol in the blood was 450 mg. per 100 cc.

The value for blood sugar was 170 mg. per 100 cc. and there was no sugar in the urine. Treatment with 1 gr. (0.065 Gm.) of desiccated thyroid was begun but the patient was unable to stay in Rochester for observation. When he was next seen three years later, the diabetes was well controlled by 12 to 18 units of a mixture of insulin and the myxedema was controlled by desiccated thyroid. The basal metabolic rate was +1 per cent.

CASE VI. This is the report of a patient who underwent total thyroidectomy in the hope of making his severe diabetes easier to manage. The case has been reported in detail by Wilder, Foster and Pemberton,[5] and is included here only because it illustrates so well the effect of myxedema on diabetes. The patient, a white man twenty-six years of age, was first seen at the clinic in 1933. Diabetes mellitus had been present for eleven years. In spite of a rigid diet and 45 units of regular insulin daily there was considerable difficulty in controlling glycosuria, and insulin reactions occurred fairly frequently. There were no signs or symptoms of thyroid dysfunction and two basal metabolic rates were +5 and +2 per cent. Fasting blood sugar measured 429 mg. per 100 cc. and the concentration of cholesterol in the blood was 208 mg. per 100 cc. On a weighed diet of 2,300 calories, containing 103 Gm. of carbohydrate, and a dose of 30 units of insulin per day, the patient before operation excreted an average of 36 Gm. of carbohydrate daily in his urine.

The patient was aware of the hazards of total thyroidectomy and the uncertainty of the results that might be obtained. At operation 10 Gm. of histologically normal thyroid tissue was removed. Some tissue was preserved at the hilus of each lobe but the amount was not more than the size of a split pea. The parathyroid glands were not disturbed. The insulin requirement rose to 65 units on the fourth postoperative day. On this day 20 Gm. of glucose were excreted in the urine and the intake was 84 Gm. Thereafter the insulin requirement dropped gradually and thirty days after operation the urine was practically free of sugar on 15 units of insulin while the diet was the same as before operation. The basal metabolic rate at this time was −29 per cent.

While at home the patient kept an accurate account of the amount of sugar in the urine and insulin taken. Ten units was the average dose which was necessary to keep his urine free of sugar.

Symptoms of myxedema appeared about sixty days after operation and 3 gr. (0.2 Gm.) of desiccated thyroid were given daily for a period of four days. The symptoms of myxedema began to regress but the insulin required on the fourth day was 30 units. Administration of desiccated thyroid was then stopped and two weeks later 10 units of insulin again kept the urine free of sugar. Thirty days later symptoms of myxedema reappeared. Three and a half months after operation the patient returned to the clinic and presented typical signs and symptoms of myxedema. The daily insulin requirement varied from eight to twelve units. The basal metabolic rate was −35 per cent. Control of myxedema, as far as gross evidence was concerned, was obtained on ½ gr. (0.032 Gm.) of desiccated thyroid daily although the basal metabolic rate did not rise appreciably. On this dose the diabetes was controlled with 14 to 16 units of insulin. The patient was reasonably comfortable but felt that he was not as well generally as he had been with only the diabetes to concern him.

Case V illustrates the effect of both hyperfunction and hypofunction of the thyroid on diabetes. Diabetes became manifest after hyperthyroidism had been present for some time. After thyroidectomy the diabetes became much less severe and, with the development of myxedema, small doses of insulin produced insulin reactions. Insulin was again needed when the myxedema was controlled although never in amounts equal to those required when hyperthyroidism was present.

Case VI is included to illustrate the effect of a complete lack of thyroid hormone on diabetes. As can be seen, myxedema in this patient produced marked amelioration of the diabetes and control of the myxedema resulted in an increase in the severity of the diabetes.

ADRENAL CORTEX AND HUMAN DIABETES

Co-existing Diabetes Mellitus and Adrenal Cortical Insufficiency (Addison's Disease). Ablation of the adrenal glands from animals is followed by a decrease of the concentra-

tion of carbohydrate in the blood, liver and muscle. Hypoglycemia during fasting is a common manifestation of adrenal cortical insufficiency in some species, including the human being. Conversion of protein to carbohydrate is impaired. The rate of oxidation of administered glucose may be accelerated. Sensitivity to insulin may be strikingly increased. The rate of absorption of glucose from the intestinal tract is decreased.

The aforementioned effects of adrenalectomy are strikingly illustrated in the diabetic animal. There is marked amelioration of the diabetic state similar to that produced by hypophysectomy. Excretion of glucose, nitrogen and ketone bodies diminishes. Sensitivity to insulin is augmented. The full intensity of diabetes can be restored by administration of suitable amounts of adrenal cortical hormones which have carbohydrate activity, such as compound E (17-hydroxy-11-dehydrocorticosterone) or compound F (17-hydroxycorticosterone).

The foregoing physiologic principles can be applied in varying degrees to patients who have co-existing Addison's disease and diabetes mellitus, as illustrated by the following case reports.

CASE VII. The patient was first examined at the clinic in October, 1942, when she was thirty-seven years of age. A paternal uncle had diabetes. At the age of fifteen years she had been treated medically for thyrotoxicosis. At the age of twenty years she had experienced an attack of acute pelvic inflammatory disease.

In 1934, at the age of twenty-nine years, she had been found to have diabetes mellitus. She had severe diabetic acidosis at the time the diagnosis was made. For the next several years she took from 30 to 40 units of insulin daily, with fair to poor control of glycosuria. Pigmentation of the hands, face and neck was first noted by the patient and members of her family in 1939. Early in 1942 she began to note failure of strength and appetite. Soon she began to experience nausea, occasional vomiting, hiccup and abdominal distress. Insulin reactions, which had formerly been infrequent, occurred almost daily. In June, 1942, it was suspected by her physicians that she might have Addison's disease in addition to diabetes mellitus, and she was treated with injections of desoxycorticosterone acetate. She continued to have insulin reactions and the daily dose of insulin was gradually decreased. In September, 1942, the administration of insulin was discontinued entirely. The urine remained consistently free of sugar.

In the initial examination at the clinic the blood pressure was 64 mm. of mercury systolic and 40 mm. diastolic. She was weak and nauseated. Pigmentation characteristic of Addison's disease was present. There were large areas of vitiligo on the arms. The urine was free of sugar and the value of the blood sugar was 40 mg. per 100 cc. The concentration of sodium in the serum was 128.7 mEq., chlorides 90.9 mEq. and potassium 5.1 mEq. per L.

Emergency treatment with intravenous infusions of solutions of sodium chloride, glucose and adrenal cortical extract resulted in simultaneous clinical improvement and reappearance of glycosuria and hyperglycemia.

Subsequent investigations gave the following results: The urinary excretion of 17-ketosteroids was 0.6 mg. in twenty-four hours. Results of a water test (Robinson, Power and Kepler) were positive in parts I and II. Repeated determinations of the serum sodium and chlorides under varying circumstances gave values as low as 119 mEq. per L. for sodium and 88 mEq. per L. for chloride. The values for serum potassium and blood urea were, for the most part, within normal limits. The value of blood sugar on numerous occasions and under varying conditions of therapy varied from 40 to 492 mg. per 100 cc. The daily urinary excretion of glucose varied from 0 to 142 Gm. Examination of the ocular fundi revealed a mild central punctate type of diabetic retinopathy.

The patient was observed in the hospital on five different occasions between October, 1942, and October, 1945. When she was treated for adrenal insufficiency with desoxycorticosterone acetate alone, she exhibited unusual sensitivity to insulin. On one occasion she experienced a severe hypoglycemic reaction eight hours after receiving 4 units of insulin. On another occasion she experienced an insulin reaction three hours after the administration of 3 units of insulin. On several other occasions she had hypoglycemic reactions without having received insulin, particularly if food was withheld for more than a few hours.

On the other hand, when her adrenal insufficiency was treated with large doses of whole adrenal cortical extract, hog adrenal extract (lipoadrenal cortex) or 17-hydroxy-11-dehydrocorticosterone (compound E), glycosuria increased and she was able to take as much as the concentration of blood sugar was sustained at a high level, glycosuria was marked, ketonuria was intense and excretion of nitrogen was significantly increased. In another study, not illustrated in Figure 4, definite effects similar to those obtained with compound E were observed

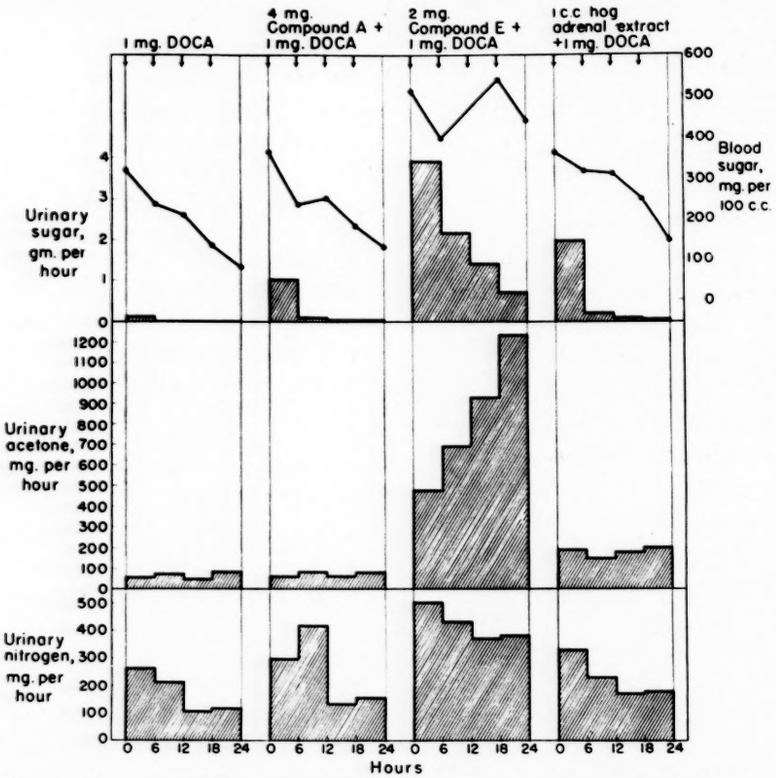


FIG. 4. Effects of 17-hydroxy-11-dehydrocorticosterone (compound E) compared to those of desoxycorticosterone acetate, 11-dehydrocorticosterone (compound A) and an extract of hog adrenal glands in Case VII. In each instance the hormone being studied was added to a basal treatment with desoxycorticosterone acetate. Data for blood sugar and urinary sugar, acetone and nitrogen during a period of fasting of twenty-four hours after withdrawal of insulin are shown.

44 units of regular insulin daily in 2 doses without experiencing symptoms of hypoglycemia.

Observations of the influence of various programs of treatment for adrenal insufficiency on the behavior of the diabetes were made during periods of fasting after withdrawal of insulin while the deficiency of salt and water of Addison's disease was controlled with desoxycorticosterone acetate. (Fig. 4.) When insulin was not administered and she fasted during treatment with desoxycorticosterone acetate, compound A or hog adrenal extract in the doses shown, the amount of sugar in the blood and urine decreased and only slight ketonuria was present. By contrast, during treatment with compound E when a larger dose of hog adrenal extract was employed.

In December, 1945, the patient became ill at home and was thought to have pelvic peritonitis. At that time her adrenal insufficiency was apparently well controlled with hog adrenal extract and desoxycorticosterone acetate, as she was in diabetic acidosis in spite of taking 20 units of regular insulin daily. She died with hyperpyrexia and clinical findings suggestive of pulmonary edema.

At necropsy, the principal findings were pelvic peritonitis secondary to bilateral pyosalpinx, and atrophy of the adrenal cortices. No cortical cells could be seen in sections of the adrenals. The

pancreas weighed 25 Gm. and grossly presented evidence of fatty infiltration. On microscopic examination the islets showed no pathologic change.

CASE VIII. A woman, thirty years of age, was hospitalized on admission to the clinic, June 29, 1946. In June, 1945, she had consulted her physician because of thirst, polyuria, weakness and loss of weight and had been found to have diabetes mellitus. Weakness had been an unusually prominent symptom at that time. The urine became free of sugar when she took 30 units of protamine zinc insulin daily for a week. It remained free of sugar without the use of insulin until October, 1945, when she had a sore throat and glycosuria recurred. Since then she had taken 20 to 30 units of protamine zinc insulin daily, and had noted a progressive failure of strength and a gradual increase in the frequency and severity of hypoglycemic reactions. In April, 1946, she had first become aware of increased pigmentation of the face and hands.

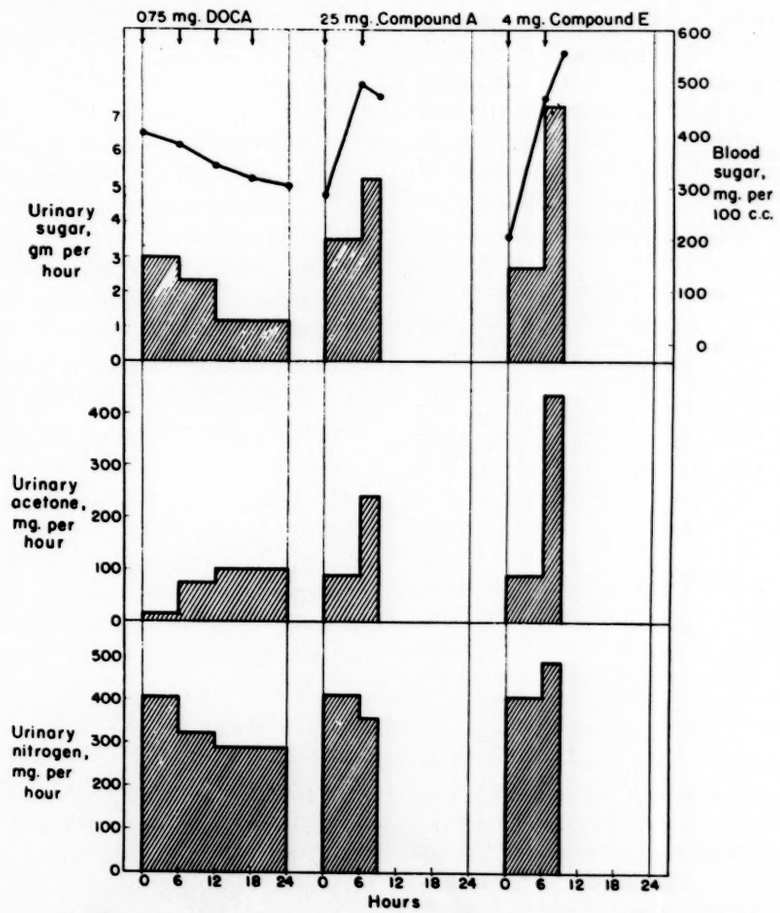


FIG. 5. Comparative effects of desoxycorticosterone acetate, 11-dehydrocorticosterone (compound A) and 17-hydroxy-11-dehydrocorticosterone (compound E) in Case VIII. Data for blood sugar and urinary sugar, acetone and nitrogen during a period of fasting after withdrawal of insulin are shown. In the latter two studies, involving the use of compound A and compound E, it was necessary to terminate the observations after nine hours of fasting because of the development of severe ketosis.

On admission to the hospital the patient presented evidences of both adrenal insufficiency and uncontrolled diabetes. The blood pressure was 90 mm. of mercury systolic and 50 mm. diastolic. She was profoundly weak and nauseated and hiccupped at frequent intervals. There was frank addisonian pigmentation of moderate degree. The urine contained sugar, grade 4, but no acetone or diactic acid. The value for blood sugar was 289 mg. per 100 cc. The serum sodium

was 126 mEq., chlorides 97.3 mEq., potassium 6.8 mEq., carbon dioxide content 24.2 mEq. per L. and the blood urea 40 mg. per 100 cc.

Subsequently additional data confirming the presence of Addison's disease were obtained. The urinary excretion of 17-ketosteroids varied between 0.5 and 1.5 mg. per twenty-four hours on several occasions. A differential count of leukocytes showed 47 per cent lymphocytes with a total count of 6,200 per cubic millimeter. Results of a water test (Robinson, Power and Kepler) were strongly positive in parts I and II. A salt-deprivation test (Cutler, Power and Wilder) had to be terminated twelve hours after it was started because of symptoms of acute adrenal insufficiency, which were promptly corrected by an intravenous infusion of solution of sodium chloride and adrenal cortical extract. A tuberculin test gave negative results.

Studies of the influence of various programs of treatment for Addison's disease on the behavior of the diabetes during periods of fasting after withdrawal of insulin, similar to the studies which had been carried out previously in Case VII, were made. During treatment with desoxycorticosterone acetate the concentration of blood sugar decreased during fasting, and glycosuria and ketonuria were of only moderate intensity. (Fig. 5.) By contrast, when Addison's disease was treated with 11-dehydrocorticosterone (compound A) or 17-hydroxy-11-dehydrocorticosterone (compound E), the diabetes was greatly intensified. In each instance severe ketosis developed within the first nine hours of fasting after withdrawal of insulin, so that it was necessary to terminate the observation and administer insulin and infusions of solutions of sodium chloride. The effects of 4 mg. of compound E every six hours appeared to be somewhat more marked than those of 25 mg. of compound A every six hours.

After the metabolic studies which have been described the patient was permitted to return home. She was in good condition taking 2 doses of regular insulin daily totaling 28 units, 1 mg. of desoxycorticosterone acetate, 1 cc. of hog adrenal cortical extract and 3 Gm. of sodium chloride in addition to that contained in her food. She died at home on February 14, 1947, several days after a severe hypoglycemic reaction.

The history in each of the foregoing cases indicated some amelioration of diabetes with the onset of adrenal cortical insufficiency. In Case VII the amelioration was marked, so that insulin was no longer necessary for control of glycosuria and, indeed, hypoglycemic reactions occurred even though insulin had not been administered. In Case VIII, on the other hand, the amelioration of the diabetes was less marked, suggesting that the patient might have had a functioning remnant of adrenal cortical tissue which was producing a sufficient supply of carbohydrate-active steroid hormones to maintain a moderately severe diabetic state.

The metabolic studies in each case indicate that the diabetic state could be greatly intensified by the administration of carbohydrate-active adrenal steroids but not by the administration of desoxycorticosterone acetate alone.

Diabetes Mellitus Associated with Hyperfunctioning Lesions of the Adrenal Cortex. Diabetes mellitus which is sometimes observed in the case of patients who have hyperfunctioning lesions of the adrenal cortices is in all likelihood due to excessive production of adrenal cortical hormones which have predominant carbohydrate activity, that is, the 11 and 11–17 oxygenated steroids. The most potent of these are 17-hydroxy-11-dehydrocorticosterone (compound E) and 17-hydroxycorticosterone (compound F), the latter having slightly stronger effects than the former.

Ingle and his associates[6–8] have produced the counterpart of human "steroid diabetes" in rats by the administration of relatively large doses of compound E or compound F. The diabetic state which is so produced has certain characteristics which differ from those of the diabetes which is commonly observed in children and young adults. (1) It is relatively insensitive to insulin, Ingle and associates having failed to control glycosuria completely in some of their rats with as much as 1,000 units of insulin daily. (2) It becomes mild when food is withheld so that glycosuria disappears. (3) Since one of the effects of the adrenal hormones which cause this type of diabetes is to stimulate the

formation of sugar from protein, it is associated with a negative nitrogen balance, even when glycosuria is minimal or absent.

The following two cases seem to be examples of "steroid diabetes" in human beings.

CASE IX. This case has previously been reported in detail by Sprague, Priestley and Dockerty.[9] A woman, forty-nine years of age, came to the clinic for examination in February, 1941. A diagnosis of diabetes mellitus had been made three years previously and the condition had been treated with insulin in doses up to 145 units daily. Hypoglycemic reactions had never occurred.

Physical examination was negative except for a large, deep, movable mass in the right upper quadrant of the abdomen. The blood pressure was 160 mm. of mercury systolic and 94 mm. diastolic. The habitus was normal, the amount and distribution of hair on the body were normal, and except for atrophic changes in the vulva and vagina, there were no abnormalities of the external genitalia or pelvic organs. The menstrual history was normal and she was still menstruating regularly. Laboratory examinations were negative except for glycosuria and a fasting blood sugar which measured 252 mg. per 100 cc.

During several days of study before surgical exploration of the abdominal mass the patient received each morning a combined dose of protamine zinc and regular insulin totaling between 30 and 68 units. As much as 28.7 Gm. of glucose were excreted in the urine in twenty-four hours. Ketone bodies were never found in the urine. There were no hypoglycemic reactions.

Surgical exploration of the abdomen was performed on March 12, 1941. A tumor of the right adrenal cortex weighing 1,550 Gm. was removed. Histologic examination revealed that the lesion was an adenocarcinoma, grade 2.

After the day of operation the urine remained consistently free of sugar. On the fifth postoperative day the value of blood sugar was 88 mg. per 100 cc. The dose of insulin was gradually reduced and it was discontinued on the sixteenth postoperative day.

All subsequent investigations of the patient's carbohydrate metabolism gave normal results. There was never any further evidence of diabetes. A glucose tolerance test performed eight months after removal of the tumor gave a normal result. Determinations of the fasting blood sugar at intervals up to eight years after the operation were all normal.

CASE X. A boy, fifteen years of age, came to the clinic on February 3, 1948, because of diabetes mellitus associated with weakness and loss of weight. Diabetes had been discovered in January, 1946. At that time it was also noted that his face was redder and rounder than formerly and pink striae had been observed on the thighs. Insulin was employed from that time until June, 1946.

From June, 1946, to December, 1947, there was a complete remission of the diabetes. The abnormal redness and contour of the face also disappeared. In December, 1947, symptoms of diabetes, associated with redness and roundness of the face and marked weakness, reappeared. Glycosuria was again found, and insulin in doses up to 80 units daily was once more employed. Even with this dose of insulin, glycosuria persisted and there were no insulin reactions.

Physical examination on admission of the patient to the clinic revealed most of the classical features of Cushing's syndrome, including hypertension, weakness, a full, round face of high color, acne, dry skin, keratosis pilaris, purplish striae, protuberant abdomen and a wasting of the arms and legs. Laboratory and roentgenologic studies disclosed hypochloremic, hypokaliemic alkalosis of marked degree, osteoporosis, lymphopenia, glycosuria and hyperglycemia. The fasting blood sugar was 245 mg. per 100 cc. The urinary excretion of 17-ketosteroids was 77.5 mg. in twenty-four hours, the beta fraction being 18.5 per cent. The urinary excretion of corticosteroids was 17.1 mg. in twenty-four hours. The latter finding eventually led to the isolation of 17-hydroxycorticosterone (compound F) from the urine, 191 mg. of purified hormone being obtained from a twenty-five-day collection of urine.[10]

The clinical diagnosis was Cushing's syndrome associated with diabetes mellitus.

Metabolic studies[11] disclosed the following significant points: (1) The diabetes was severe and relatively insensitive to insulin, glycosuria being incompletely controlled with doses of insulin ranging from 20 to 130 units daily. (2) Balances for nitrogen, calcium and phosphorus were negative. (3) Glycosuria virtually disappeared during fasting even though insulin was withheld.

The death of the patient after surgical resection of the right adrenal gland, which was hyperplastic, precluded further metabolic study. At necropsy, markedly hyperplastic adrenal cortices were found, the remaining portion of the right adrenal gland weighing 5 Gm. and the left adrenal, 29 Gm.

The foregoing two cases are presumably instances of "steroid diabetes" in man, analogous to that produced by Ingle and co-workers in rats by the administration of large doses of carbohydrate-active adrenal steroids. The evidence in support of this analogy was particularly strong in Case x, for 17-hydroxycorticosterone (compound F), an adrenal steroid hormone known to have strong carbohydrate activity, was isolated from the urine in considerable quantities.[10] Furthermore, the diabetes in this case was shown to have the characteristics of "steroid diabetes" in animals; namely, insensitivity to insulin, negative nitrogen balance even when glycosuria was minimal and mildness during fasting.

In Case IX the evidence that the diabetes was due to excessive production by the adrenal cortical tumor of hormones which have carbohydrate activity, rather than to primary insulin deficiency, was also strong. All evidences of diabetes disappeared soon after removal of the tumor, just as it does in rats with steroid diabetes when the administration of the diabetogenic adrenal steroid is interrupted. It can therefore be reasonably presumed in this case that the diabetes was due solely to overproduction of carbohydrate-active adrenal steroids, and that islet function was basically within normal limits.

SUMMARY

As is true in the experimental animal, the behavior of diabetes mellitus in the human may be markedly altered by either hypofunctioning or hyperfunctioning lesions of the anterior pituitary, thyroid or adrenal cortex. In general, hypofunctioning lesions of these glands of internal secretion ameliorate existing diabetes while hyperfunctioning lesions intensify it. Hyperfunction of the anterior pituitary due to eosinophilic adenoma, or of the adrenal cortex due to tumor or hyperplasia may apparently be the sole cause of diabetes in rare cases.

Ten cases in which diabetes mellitus was associated with hypofunctioning and hyperfunctioning lesions of the aforementioned glands have been presented. The basic physiology concerned in the alteration of the diabetic state by such lesions has been considered briefly. It is emphasized that the observations which were made in these cases are not applicable to the majority of cases of diabetes, in which evidences of endocrine disease other than the diabetes itself are usually absent.

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Pregnancy Complicating Diabetes*

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DURING the past fifteen years a study has been made at the George F. Baker Clinic of the New England Deaconess Hospital to determine possible causes and the means to prevent the high fetal wastage in diabetic pregnancies. The following report is a summary of the experiences with 439 viable diabetic pregnancy cases in which assays for one or more of the sex hormones of pregnancy were determined. Viability in the infant was defined by weight, namely, in excess of 960 Gm. This series of 439 includes all consecutive cases under personal observation. Excluded from the report are consultation cases treated elsewhere and patients reporting to the clinic for delivery but arriving too late for significant studies for sex hormone excretion.

The series appears to be unique because it is characterized by the number of primiparae, the number of patients in whom the onset of diabetes occurred in childhood and youth and those in whom the duration of diabetes is long. Primiparae numbered 57 per cent of the series. The onset of diabetes had occurred under the age of twenty years in more than half (58 per cent) and the duration was long, exceeding ten years in 50 per cent.

Although maternal mortality was low, for there was only one death or a case mortality of 0.2 per cent, fetal fatalities numbered 78, or 18 per cent. The maternal death was technically so classified only. It occurred fifty days after delivery and was proved by autopsy to be due to infectious hepatitis. These vital statistics as well as those reported elsewhere indicate that fetal not maternal survival constitutes the problem when pregnancy complicates diabetes.

Abnormalities in the obstetric course were common and included eclampsia four times (1 per cent); an additional seventy-six patients (17 per cent) had hypertension and albuminuria; eighty (18 per cent) had hypertension alone and thirty-four (8 per cent) albuminuria alone. Nearly one-half the number thus had evidence of hypertensive disorders or renal disease. Placenta previa occurred once; premature rupture of membranes before the twentieth week with continuous loss of amniotic fluid for weeks and months occurred four times. Two other deviations from normal obstetric courses were frequently seen, namely, irritability of the uterus and hydramnios. These complications occurred in varying degrees in nearly all patients.

Diabetic crises, on the other hand, were infrequent. Coma, defined as a lowering of the CO_2 content of the blood to 9 m.Eq., occurred in eight patients only, or 2 per cent, and hypoglycemia of severity in four, or 1 per cent.

The fetal fatalities are summarized in Table 1. Of the seventy-eight fetal deaths, thirty-four were stillbirths and forty-four occurred in the early neonatal period. From Table 1 it appears that fetal fatalities have been influenced in varying degrees by (1) poor control of maternal diabetes, (2) the occurrence of congenital fetal defects, (3) the degree of maternal vascular disease, (4) prematurity, (5) duration of diabetes, (6) its age of inception and (7) the imbalance of the sex hormones of pregnancy.

Diabetic coma which may be taken as the measure of the maximum degree of poor control of diabetes coincided with 5 per cent of the fetal fatalities. Indeed, only two infants in this series survived a bout of dia-

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betic coma. The harmful influence appeared to be more in relation to the occurrence of stillbirths than it did to neonatal deaths, for it coincided with intrauterine fetal death in 10 per cent of such cases. In only 2 per cent of the neonatal deaths was a bout of coma coincidental with the fatality. The reverse situation, hypoglycemia of severity, did not coincide with fetal fatalities. Convulsive episodes, one in an epileptic and the other during the administration of lithium salt substitute, coincided with an intrauterine death each.

TABLE 1

RELATIVE FREQUENCY OF CONDITIONS ASSOCIATED WITH SEVENTY-EIGHT FETAL DEATHS

A. Total:	Per cent
Eclampsia	1
Diabetic coma	5
Congenital anomalies	9
Arteriosclerosis	
Pelvic	20
Total	33
Hypertension and/or albuminuria	46
Prematurity	46
Long duration of diabetes (more than 10 years)	52
Early age at onset of diabetes (under 10 years)	66
Imbalance of sex hormones	97

B. Comparison of Relative Frequency of Conditions Associated with Fetal Deaths Classified As Stillbirths and Neonatal Deaths:

	Stillbirths Per cent	Neonatal Deaths Per cent
Eclampsia	0	2
Coma	10	2
Congenital anomalies	3	15
Arteriosclerosis		
Pelvic	24	16
Total	33	42
Hypertension and/or albuminuria	71	52
Prematurity	32	66
Long duration of diabetes	73	37
Early age at onset of diabetes	74	60
Sex hormonal imbalance	100	97

The most tragic of the harmful influences —tragic because it is unpredictable—is the occurrence of the congenital fetal defect. This coincided with 8 per cent of the fetal fatalities. Only one defect, or 3 per cent, was demonstrated in a stillborn infant. The lethal defect in this infant was the absence of both kidneys. Congenital anomalies coincided with 15 per cent of the neonatal deaths and included one instance each of hemorrhagic disease of the newborn, multiple skeletal defects and defect of the skull incompatible with survival, congenital heart, congenital pneumomediastinum and anencephaly.

The most devastating of the harmful effects because of its influence in early as well as in late pregnancy periods was the degree of maternal vascular disease. Some evidence of arteriosclerosis was found with 33 per cent of the fetal fatalities, 33 per cent of the stillbirths and 42 per cent of the neonatal deaths. When arteriosclerosis in the young diabetic had progressed so far that the pelvic blood vessels were calcified, the fetal survival for the entire period of pregnancy was 10 per cent only. In such a group, when everything which appears to promote successful outcome of diabetic pregnancies was carried out, the fetal survival in twenty-eight viable cases rose to 50 per cent. When the arteries of the pelvis are shown to be calcified by x-ray, involvement of the uterine and ovarian arteries is inferred. These are the first arteries in the body of the normal woman to undergo sclerotic changes and it would be unlikely that in the diffuse sclerosing process of the diabetic they would be expected. Although the calcification demonstrable by x-ray suggests the medial type of sclerosis, internal changes and occlusive vascular disease characteristic of diabetes are also inferred. No uteri in this series of patients have been observed at the time of delivery. Hysterectomies have not been performed and the one patient who came to autopsy fifty days after delivery did not have calcified pelvic arteries. The most striking case in this group is that of E. R., Case 1469, who died at the age of forty in December, 1948. Her death due to arteriosclerotic cardiorenal disease occurred after thirty years of diabetes. Pregnancies had occurred ten years, eight years and six years prior to death. The first pregnancy terminated successfully in a living birth and the

child is well today. On autopsy the endometrium, myometrium and the arteries were described as those of a woman of seventy years of age.

The importance of the vascular problem in obstetric diabetes cannot be overemphasized. A survey of our former diabetic children, defined as patients in whom the onset of diabetes occurred under the age of fifteen, who then survived twenty years or more of diabetes, showed that 93 per cent had some evidence of vascular disease. Such lesions do not become manifest often under the age of twenty years and are rare when diabetes is of less than ten years' duration. The specificity of the site of the attack in those in whom the disease starts in childhood is of great importance in the obstetric problem because destructive effects are seen in the retina and in the kidneys most commonly. (Table II.)

Hypertension and albuminuria, or hypertension alone or albuminuria alone, coincided with 46 per cent of the fetal fatalities and prematurity coincided with 46 per cent. In only 29 per cent of the stillbirths was evidence of hypertension or albuminuria lacking and 71 per cent of the cases had such abnormalities. To a lesser degree, but also in half the cases, hypertension, albuminuria or both were associated with neonatal deaths. Of greatest importance from the viewpoint of the obstetric and medical management of the patient was the fact that 68 per cent of the stillbirths occurred late in pregnancy, from the thirty-sixth to the fortieth week, whereas only 34 per cent of the neonatal deaths occurred after the thirty-fifth week. Long duration of diabetes and early onset of the disease were associated with more than half of the fetal fatalities, namely, 53 and 66 per cent, respectively, the harmful influence being shown more in relation to stillbirths than to neonatal deaths.

The most frequent of the harmful influences, however, was the imbalance of the sex hormones of pregnancy, coinciding with 97 per cent of the fetal fatalities and occurring in 90 per cent of our entire series of patients. The abnormalities included a rise of chorionic gonadotropin between the twenty-third and thirty-fifth week of pregnancy to a level of 200 rat units per 100 cc. of serum or above, a lowering of the excretion of estrogen with abnormal ratios of the degradation products and lowered excretion of pregnanediol glucuronidates.

TABLE II
DURATION OF DIABETES AND VASCULAR COMPLICATIONS

Duration of Diabetes (Years)	Retinal Arteriosclerosis Per cent	Retinitis Per cent	Calcified Arteries Per cent	Nephritis Per cent
Under 10	3	3	3	2
10–14	10	10	8	6
15–19	50	45	40	30
20 and over	85	75	70	40
Age in Years and Vascular Complications				
Age in Years				
Under 20	8	2	5	2
20–29	60	50	50	30

From the foregoing it is evident that our problem must concern the investigation of the causes and the means to prevent premature delivery of the infant of the diabetic mother prior to the period of its viability (which appears to be later than that of the normal woman) and, secondly, the termination of the pregnancy at the point of viability and before the dreaded late intrauterine accident can occur.

In addition to the chemical grading of patients, which has been previously reported upon, in 1948 clinical grading of the obstetric diabetic patient was made. This evaluation was based upon the pre-pregnancy state and the designation was alphabetical, A through F. Classes A through E referred to fetal risk and F to maternal risk. From the previous discussion it is evident that age at onset of diabetes, duration, severity and degree of maternal vascular disease all influence the fetal survival unfavorably. Renal disease carries with it maternal hazards in the diabetic population

as well as the obstetric population at large. Therefore, the grading of the patients was as follows:

Class A, with highest chance for fetal survival, includes patients in whom the diagnosis of diabetes was made upon a glucose tolerance test which deviates but slightly from the normal. Such patients require no insulin and little dietary regulation. They numbered only 5 per cent of our 439 cases.

Table III
SUMMARY OF 433* CASES DIVIDED ACCORDING TO SEX HORMONAL BALANCE

Sex Hormonal Balance	No. of Cases	Eclampsia Per cent	Hypertension and Albuminuria Per cent	Delivery Prior to 34th Week Per cent	Fetal Survival Per cent
Abnormal	89	3	26	17	58
Corrected	297	0.3	16	9	89
Normal...	47	0	6	0	95

* Cases of placenta previa—1; premature rupture of membranes—4; erythroblastosis—1 excluded.

Class B (29 per cent of this series) included patients whose diabetes started in adult life at the age of twenty or above, and those in whom the duration of the disease was less than ten years and those who were free from vascular disease.

Class C (44 per cent of this series) included patients whose diabetes was of long duration, between ten and nineteen years, those in whom the onset of diabetes occurred between ten and nineteen years of age or those who had minimal vascular disease, such as retinal arteriosclerosis or calcification of the vessels of the legs alone.

Class D (14 per cent of the group) included patients whose diabetes was of twenty or more years' duration, or whose onset occurred under ten years or who had more evidence of vascular disease such as retinitis, transitory albuminuria or transitory hypertension.

Class E included patients in whom calcification of the pelvic arteries was demonstrable by x-ray. They numbered 7 per cent of our series.

Class F (1 per cent) included all patients with nephritis.

In addition to the clinical classification the cases were divided as previously into three classes upon a chemical basis as follows: first, forty-seven cases in which no examination for chorionic gonadotropin exceeded 200 RU /100 cc. of serum between the twenty-third and the thirty-fourth week and /or in whom the pregnandiol excretion did not fall below the level of minimal normal excretion, according to the curve of Venning and Browne; second, eighty-nine cases which did show chemical evidence of abnormal balance of the sex hormones of pregnancy; third, 297 cases which received sex hormone treatment. The fetal survival of the two first groups, shown in Table III, was as follows: 58 per cent when the hormonal balance was abnormal and uncorrected and 95 per cent when the hormonal balance was spontaneously normal. With added duration of diabetes and the incidence of diabetic arteriolarnephrosclerosis, the evaluation of pre-eclampsia in the group has become difficult. Hypertension and albuminuria occurred in 26 per cent of the patients in whom the hormonal balance was abnormal and in 6 per cent of those in whom it was spontaneously normal, and spontaneous delivery before the thirty-fourth week occurred in 17 per cent of the patients in whom the hormonal balance was abnormal and in none of those in whom the hormonal balance was completely normal.

In order to prevent the high fetal wastage in obstetric diabetes, premature delivery and pre-eclampsia, the management suggested by the experience with the 439 cases includes, first, good treatment of diabetes; second, substitutional hormonal therapy; third, the correction of edema and hydramnios; fourth, premature delivery and, fifth, special care of the infant whose viability was obviously not that of the infant of the normal woman of comparable period of gestation and size.

The dietary prescription included calories adequate to meet the metabolic needs of mother and child, namely, 30 calories per Kg. of body weight throughout pregnancy. The protein intake was high, namely, 2 Gm. per Kg. of increasing body weight, and the carbohydrate liberal, from 180 to 250 Gm. daily. The fat was prescribed merely to complete the caloric prescription.

The plan for insulin therapy has been based upon the prevention of accidents resulting from the extreme glycosuria due to the low renal threshold. With nearly normal levels for blood sugar these women may excrete 100 to 150 Gm. of sugar in twenty-four hours. When utilization of glucose falls below 100 Gm., ketosis sets in easily. Attempts to correct glycosuria with single massive doses of insulin favor the development of severe hypoglycemic shock. In the past a basic dose of long-acting insulin has been administered before breakfast and supplemented by three or four additional doses of rapidly acting insulin before breakfast, before lunch, before supper and even at bedtime. Twenty-four patients were adjusted to modified protamine, NPH-50, insulin and of this number 60 per cent were successfully treated with a single dose in twenty-four hours.

The plan for hormonal therapy at present is influenced by our clinical as well as chemical classification. A wide variety of forms of estrogenic and progestational therapy have been employed. Natural and synthetic estrogens included stilboestrol, progynon B, benzestrol and premarin. In a few patients oreton was used in place of progesterone. Administration has included oral route, parenteral injection and implantation of pellets. The duration of therapy has varied from three to thirty-two weeks. Adequate therapy is now defined as continuous and daily, certainly not less often than every second day.

From our experience the present plan for sex hormone therapy has been developed as shown in Table IV: Class A none, Classes B and C from 5 to 50 mg. of stilbestrol and proluton daily, Class D from 10 to 75, Classes E and F from 25 to 125 mg. of each intramuscularly daily.

Therapy is started by choice as early as the sixth week and continued until the day before delivery. The husbands are taught the administration of the intramuscular injections, for daily intramuscular injections of stilbestrol and progesterone are considered the most efficacious form of treatment. Deviations from normal hormonal excretion levels have been used as the guide for regulation of doses of therapy. Thus if the level for chorionic gonadotropin remained high and/or the excretion of pregnandiol low, the patient has been advised to advance her schedule to that of the next four-week period. Deviations from normal clinical course, such as abnormal gain in weight, edema, hydramnios, hypertension and/or albuminuria, have all been used as indications, too, for advancing therapy.

TABLE IV
SEX HORMONAL THERAPY IN MG. OF STILBESTROL AND PROLUTON ACCORDING TO WEEKLY PREGNANCY AND CLINICAL CLASSIFICATION

Week of Pregnancy	Stilbestrol and Proluton in mg. According to Class			
	A	B and C	D	E and F
6–19	0	5	10	25
20–23	0	10	15	50
24–27	0	15	25	75
28–31	0	25	50	100
32 and up	0	50	75	125

The effect of sex hormonal therapy upon fetal survival was most favorable. The survival rate rose from 58 to 89 per cent. Today it has become difficult to evaluate the hypertension and albuminuria seen in the long-duration young diabetic. Since 1940 every juvenile patient surviving fifteen years of diabetes and coming to autopsy at the Deaconess Hospital has shown intercapillary glomerulosclerosis. Pregnancy may merely reveal the latent form of vascular nephritis. However, it is our clinical impression that the typical pre-eclampsia

which was seen in the shorter duration cases prior to 1936 is seen today but rarely. The incidence of hypertension and albuminuria fell from 26 to 16 per cent and premature delivery before the thirty-fourth week from 17 to 9 per cent in the 297 patients treated continuously with substitutional hormonal therapy prior to the twentieth week.

Although no side reactions were observed, fifty consecutive patients treated with a special form of stilbestrol developed hyperplastic endometritis, requiring dilatation and curettage on one or more occasions and in some instances repeated blood transfusions.

In our experience the use of oral stilbestrol alone was unsatisfactory. Lack of absorption was feared. Each pregnancy in a diabetic after ten years' duration is a premium; therefore, those started with it were transferred usually to parenteral administration because of the frequent occurrence of abnormalities in the clinical and chemical course. When oral stilbestrol was administered, the dose range was from 25 to 350 mg. daily.

Supplementing hormone therapy and directed against the disturbance of water balance, manifested by edema and hydramnios, was the prescription of ammonium chloride in doses from 4 to 20 Gm. daily. (The latter was self-prescribed.)

Patients whose diets were relatively low in sodium, especially in sodium chloride, were advised through the omission of table salt, the use of fresh butter, salt-free breads and fresh vegetables. Sodium bicarbonate was forbidden.

The plan for delivery of the diabetic was influenced by our experience with stillbirths and our concept of diabetes and of the diabetic pregnancy. Rapid sex maturity is characteristic of diabetes in childhood. Rapid aging is characteristic of the disease in any period of life. This process of rapid maturity and rapid aging appears to be characteristic of the diabetic pregnancy. The large size of the fetus and the placenta, the fetal fat, growth of hair and nail development are all suggestive of the maturing process. The intrauterine death or the premature termination of the pregnancy appears to be another manifestation of aging. The former may even be considered as comparable to gangrene in the young diabetic similar to the vascular changes in the eye and kidney. Since 68 per cent of the stillbirths occurred after the thirty-fifth week, premature delivery was elected. By the method of trial and error the thirty-eighth week was sought, but hypertension, albuminuria or progressive hydramnios are indications for an earlier delivery. Deviation from normal hormonal balance have not been used as guides for the timing of delivery.

Cesarean section has been elected if the cervix has not been effaced. In fact, such deliveries have been done in 68 per cent, and 32 per cent only of these patients were delivered by the normal route. Cesarean sections have been done under spinal anesthesia without preliminary medication. An infusion of 1,000 cc. of 10 per cent glucose in distilled water is administered preoperatively and again six to eight hours after delivery. If long-acting insulins are used, the last dose of insulin of any type in a planned delivery is given twenty-four hours prior to it. Normal deliveries are conducted under spinal anesthesia. Sedation is held to minimal levels of 3 gr. of seconal and $\frac{1}{100}$ gr. of scopolamine.

The care of the infant prenatally includes, when possible, the correction of those abnormalities in which the infant of the diabetic mother differs from the infant of the normal woman. The differences included the large size, icterus, respiratory embarrassment, instability of the blood sugar, splanchnomegaly and excessive erythropoesis of the liver and spleen.

In the past, 80 per cent of the infants of diabetic mothers exceeded the expected weight for the period of gestation. Irrespective of gestation period 68 per cent of the infants in this series weighed less than 8 pounds, 32 per cent more than 8 pounds, 15 per cent more than 9, and 7 per cent only more than 10 pounds. The large size of the infant appears to be contributed to by three

factors: (1) edema, (2) obesity and (3) the splenomegaly.

Instability of the blood sugar rather than true hypoglycemia appears to be characteristic of the infant who may show relative hyperglycemia at birth followed by precipitous fall of blood sugar in four hours to a level of 40 mg. or below and subsequently a spontaneous rise of blood sugar in another four hours. Congenital anomalies complicated 80 per cent of these infants but in only 10 per cent were they severe and in less than 2 per cent of the cases lethal defects occurred. Respiratory difficulty of the infant appears to be associated with an excess of fluid in the upper air passages and lungs. Better control of maternal diabetes to prevent obesity and instability of the infant's blood sugar, better control of the disturbed water balance by high protein diets, salt restriction, ammonium chloride and sex hormonal therapy, better control of hormonal imbalance to prevent the irritable uterus, premature delivery and pre-eclampsia have all been sought.

The postnatal handling of the infant has been reported in detail by Gellis, White and Pfeffer.[1] It is directed against the respiratory difficulty. The clinical picture of the first few hours after delivery of those infants not progressing satisfactorily is the following: At birth the infant usually cries well and vigorously. It appears to aerate satisfactorily but within one or two hours exhibits a complaining cry. Evidence of costophrenic and intercostal retraction are observed. Bouts of cyanosis, apnea and sweating follow, and death may ensue eighteen to thirty-six hours after delivery. Autopsies have shown little evidence for adequate cause of death except for the atelectasis of the lungs. The postnatal handling of these infants now includes (1) postural draining; (2) aspiration of the upper air passages with suction and a No. 10 catheter; (3) aspiration of the stomach with suction and a No. 10 catheter and (4) the placing of the infant in an oxygen incubator where it will remain for a period of five days. Dehydration is accomplished by the postponement of parenteral or oral fluid for a period of forty-eight hours. A striking reduction in morbidity has followed these procedures.

The postpartum course of the mothers has usually been uncomplicated. Hypoglycemia has occurred infrequently only. Lactation has seldom been adequate. There have been four instances of thrombophlebitis, one of pelvic peritonitis and one of postpartum hemorrhage. The diabetic susceptibility to pyelonephritis has been evident in this group, but otherwise the postoperative, postdelivery course has been relatively uncomplicated.

A follow-up of the mothers shows that two (0.5 per cent) subsequently developed carcinoma. Case 13335 developed carcinoma of the breast and Case 27580 carcinoma of the esophagus. Neither of these patients had received hormonal therapy. Four of the patients subsequently died, three of cardiorenal disease and one of diabetic coma. A few have exhibited striking increase in tolerance for carbohydrate and no increase in severity of diabetes has been noted.

The follow-up of the infants has shown that clinical diabetes developed once. In this instance the child of two diabetics showed the classical signs and symptoms of diabetes at the age of six years. Another patient not in this series had a glucose tolerance test which deviates slightly from the normal. Except for the high incidence of congenital defects, most of which have been slight in character, and obesity noted most commonly at the age of six, the course of the infants has been normal.

Much that is controversial still exists in this problem of pregnancy complicating diabetes. That the clinical course in the obstetric diabetic patient is abnormal and that the fetal survival rate is significantly low are now two facts agreed upon by most students of the problem. In our experience in addition to sex hormonal imbalance, duration of diabetes and its coincidental vascular problems had an unfavorable effect upon the course and the fetal survival rate. Although the pre-diabetes or latent diabetes may have a harmful effect, it is

not comparable to that of long-standing diabetes. When diabetes had existed for more than twenty years, the fetal survival rate in patients receiving treatment for diabetes alone for the entire period has been only 20 per cent; and when vascular disease had progressed so far that the pelvic arteries were calcified and the treatment employed was that for diabetes alone, in our experience, the fetal survival was only 10 per cent.

The controversial points include an explanation of the mechanism, particularly which of the endocrine glands is primarily at fault, the placenta, the pituitary, the adrenal or all three. Abnormalities of placental sex hormonal balance have been demonstrated. Normal or elevated excretion of 17-ketosteroids, normal eosinophile count in treated cases suggest that in this group the function of the pituitary and the adrenal cortex at least in some respects are normal. With failure of sex hormonal balance, overfunction of the pituitary and subsequent overfunction of adrenal cortex is not an illogical theory.

Controversial, too, is the explanation of the size, the edema and the splanchnomegaly in the infant. Is it the response to pituitary, adrenal, cortical or chorionic gonadotropin, or perhaps to all three? Still more controversial is the concept of therapy. Is it stimulating or replacement? Clinical experience suggests the latter. Newer methods for assays of estrogen may in a short time solve this problem.

If we consider that the background favoring normal pregnancy includes normal function and structure of the pituitary, ovaries, uterus, placenta, liver and enzyme system, it is little wonder that the clinical course in the diabetic is abnormal and the fetal survival low; for the kidney in the young diabetic has revealed a latent vascular disease, the enzyme system of the diabetic is under suspicion, the function of the liver can be altered by abnormal deposition of glycogen and fat, the uterus and ovaries are those of suspicion, the placenta has failed in its production of sex hormones and, without the inhibiting influence of estrogen and progesterone, pituitary overactivity may occur.

Thus diabetes through its disturbed metabolism, hormonal imbalance, the transmission of congenital defects and vascular disease does have a profound effect upon the course of pregnancy and the structure and behavior of the child. The disturbed metabolism and the hormonal imbalance are the correctible parts of our problem; and although the expected fetal survival in diabetes today is 90 per cent, only when the entire genetic and vascular problem of diabetes is solved will our experience be equal to the best in non-diabetic, obstetric and pediatric experience.

REFERENCE

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Arteriosclerosis and Diabetes*

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THE relationship between diabetes and arteriosclerosis is a particularly intimate one. Arteriosclerosis, which can no longer be considered a disease exclusively of the second half of life, is being shown more and more to occur in the relatively young, particularly in diabetics. Additional data are needed, however, before we may say that severe or uncontrolled diabetes or ketosis leads directly to more extensive arteriosclerosis than would develop in mild or controlled forms of the disease.

Outstanding contributions toward the present day viewpoint have come from the observations of Dolger[35] who showed how few diabetics escape vascular lesions after fifteen or twenty years of the disease; of Dock[14] and others who called attention to the relative frequency of coronary arteriosclerosis and infarction in the young; and of Priscilla White[1] and associates, who went "all the way" in showing the high incidence of vascular lesions in the young and in very young diabetics. We now seem justified in speaking of the universality of arteriosclerosis in diabetes.

The pathologist finds it convenient to divide arteriosclerosis into three types: (1) atherosclerosis, which is considered to be essentially a disease of the intima, (2) medial sclerosis, the Moenckeberg's type[42] which in the main involves the media and (3) arteriolar sclerosis, which also includes intercapillary renal lesions. While all three are found both in the non-diabetic and in the diabetic, they occur much earlier and more extensively in diabetics. It is atherosclerosis with its intimal plaques that leads to coronary lesions and that in our day is of utmost clinical importance. Studies of these plaques in both their early and advanced stages have thrown some light on the mechanisms at work in the pre-thrombotic states but much more is yet to be learned along these lines. The pathologist would like to be able to tell us whether the cholesterol deposits are primary or secondary and whether they are of endogenous or exogenous origin, but he does not have sufficient evidence to supply the final answers.

Medial calcification, in the main, consists of deposits of calcium in the media of muscular arteries, particularly in those of the lower extremities. While the changes which precede calcium deposits are not too well understood, we do know that they are more complex than simple deposition of fat. Of clinical importance is the fact that medial calcification does not narrow the lumen of a vessel. That is why a diabetic may have marked medial calcification which does not lead to vascular narrowing and subsequently to gangrene.

DISTRIBUTION OF ARTERIOSCLEROSIS IN ANIMALS AND MAN

Arteriosclerosis is largely a human disease but is also found in carnivora and herbivora. It occurs in mammals, lower vertebrates and birds, more so in some species than in others. It is not common in monkeys, cats and dogs but does occur not infrequently in cows, horses, marsupials, parrots and shore birds which show medial sclerosis and plaques. Arteriosclerosis is not uncommon in chickens and geese fed or overfed for market. Physically active animals show less,

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inactive birds like the goose and parrot show more arteriosclerosis.

Many and varied accounts have been written on the incidence of arteriosclerosis as well as hypertension in certain races and tribes of mankind the world over. Arteriosclerosis is notably absent among the poorer classes in Southern China, in certain regions in India particularly among vegetarians, in the Kenya Colony of Africa, in Puerto Rico and in the Eskimo. The Chinese referred to live largely on rice, with very little animal protein and animal fat. Arteriosclerosis is uncommon in Mohammedans who do not eat meat and in Puerto Rico where the diet is low in animal protein and fat. Necropsies in Okinawans by Steiner[31] revealed sclerosis of the aorta in only 7 of 150 autopsies and complications and sequelae of arteriosclerosis were not seen at all. There were no cases of coronary occlusion. The diet of the Eskimo is not blubber as is commonly stated; actually he depends on the viscera and muscle of animals for his daily food. Kean and Hammill[39] in a recent report on the anthropathology of hypertension find that in certain African tribes blood pressure does not increase with advancing years as it does in this country and in Europeans. This was also true for groups of poor Chinese who live on sparse diets but not so true for the wealthier ones. Panamanians have little hypertension and they show no increasing pressure with advancing years. Zuni Indians have low arterial pressure. All of this is related more or less to the problem of arteriosclerosis.

ETIOLOGY OF ARTERIOSCLEROSIS

Here we would do well to consider the long and patient studies of Timothy Leary, who believes that atherosis (and arteriosclerosis) is essentially a metabolic disease. Human beings have a limited capacity to destroy or excrete cholesterol, which accumulates in the blood and tissues just as uric acid does in the tophi of the joints and tendons of persons with gout. Cholesterol combines with fatty acids to form cholesterol esters. According to the concept of Leary, atherosclerosis is due to production of crystalline cholesterol esters during periods of excessive ingestion of cholesterol in the following sequence: (1) cholesterol is esterified in the liver; (2) it is removed from the liver by Kupffer cells functioning as phagocytes, carrying the crystalline esters through the lungs into the systemic circulation, finally invading the arterial intima and (3) these crystalline esters, Leary contends, are just as irritating to the intima as silica is to lung tissue in silicosis. Leary contends that in this way deposit of fats leads to calcification, distortion of the artery and finally to the typical late effects and sequelae characteristic of arteriosclerosis.

Wilens considers nutritional factors of major importance in the etiology of atherosclerosis and arteriosclerosis. He notes that only too often lesions referred to as arteriosclerosis actually are of the atherosclerotic type. Included among the clinical consequences of these atheromatous lesions of the intima are angina pectoris, apoplexy and gangrene of the extremities, all of which are characterized by marked narrowing of the vascular channels. As a result of his studies Wilens is inclined to believe that such lesions might be prevented even though they cannot be healed or made to disappear. Wilens has observed histologic evidences of improvement or reversion of the lesions under certain conditions and believes that such lesions might even be brought under clinical control. During periods of marked loss in weight, says Wilens, the lipid content of intimal plaques may diminish or disappear. At necropsy he found that 67 per cent of persons without terminal weight loss had atherosclerosis while of those who had lost considerable weight only 38 per cent showed a comparable degree of atherosclerosis. Weight loss of only a few months' duration may be sufficient to cause reduction or withdrawal of lipids with a reversal of the atherosclerotic process. At the same time Wilens is not prepared to accept the dictum that this disease is altogether a disorder of nutrition, or to be more specific, a primary disorder of cholesterol metabolism.

Instead he proposes that the excess lipid material in the vessel wall might be of endogenous rather than of exogenous origin. Along with cholesterol, such lipids as phosphatides and neutral fats also are present in atheromatous lesions.

It has been realized for many years that infection is not an important factor in the etiology of arteriosclerosis and everything that is known bears out that viewpoint. It is known that during certain acute infections the blood cholesterol levels fall. During convalescence there is an up-and-down phase after which the formerly normal levels are re-established. Chronic infections, notably tuberculosis, are not productive of arteriosclerosis; in fact, the tuberculous subject is strikingly free of arteriosclerotic lesions at necropsy.

In so far as endocrine disturbances are concerned in their relationship to arteriosclerosis, not enough is known concerning the function of the individual endocrines, of their various combined effects, their action and their interactions. It is known that testosterone and estradiol inhibit hypercholesterolemia and atherosclerosis in rabbits. Pancreatectomy is followed by diabetes and diabetes is followed by arteriosclerosis. Radiation-induced or surgical thyroidectomy is followed by myxedema which in turn is followed by high cholesterol and atheromatosis. Thyrotoxicosis or thyroid extract in large doses reduces hypercholesterolemia and atheromatosis.

Age no longer is considered the dominant factor in arteriosclerosis. The decrescent period of life is the time when arteriosclerosis is most frequently noted but it is not duration of the life span which of itself is responsible. Arteriosclerosis occurs in time but it is not caused by time. The processes behind arteriosclerosis will in all probability be found to be biochemical and physical.

Sex has been considered an important factor in predisposition to arteriosclerosis. While it seems that in non-diabetics there is more peripheral vascular disease in males than in females, in diabetics the number of cases of foot gangrene that we see is about the same in both sexes. Obesity is much more prevalent in the female. These facts, of course, serve to emphasize the importance of diabetes and obesity as related to arteriosclerosis.

Occupation has been considered significant in this connection; if this means anything at all, it is recognition of the fact that mechanical strain or injury, wherever and however it occurs, is added insult which quickens the cycle of pathologic events that follow. Wilens, as others before him, emphasizes the importance of intravascular pressure plus the element of gravity which comes with the vertical posture. Intimal plaques are found more commonly in arteries in which the blood pressure is higher because of the upright position of the body.

Inheritance is undoubtedly an important factor in arteriosclerosis. The importance of family history in diabetics with vascular disease needs no emphasis. It is our experience that the diabetic in whom we find advanced arteriosclerosis frequently gives a history of cardiovascular disease in his antecedents. He also presents other evidences of the diabetic "anlage." The diabetic with manifestations of impending gangrene in his misshapen, calloused and bunioned feet will almost invariably tell the doctor, if the doctor will enquire, that his or her father or mother had feet or toes just like his own. The experienced clinician has long realized the importance and frequency of the inheritance factor in hypertension, arteriosclerosis, coronary disease and peripheral vascular disease. The inheritance factor in xanthomatosis and hypercholesterolemia is likewise well known. Here the studies of Wilkinson[40] in essential familial hypercholesterolemia are of interest. Wilkinson records four generations including 350 individuals among whom 35 manifested the syndrome of high blood cholesterol, xanthoma tuberosum, valvular heart disease, angina pectoris and electrocardiographic changes. Comparable findings were recently reported by Boas, Parets and Adlersberg[27] in

122 cases of proved coronary atherosclerosis before the age of fifty.

Overnutrition and obesity, whether the result of excessive feeding or abnormal heat conservation or suboxidation, can be shown statistically to be conducive to arteriosclerosis. In the obese hypercholesterolemia is twice as common as in the non-obese. As Wilens said, a thin person of fifty has less sclerosis than a fat one at the age of forty. Hypercholesterolemia is a common finding in obesity, hypertension, lipoid nephrosis, myxedema and in uncontrolled diabetes. In our own experience when a diabetic in the hospital is brought under satisfactory control, in most if not all cases the blood cholesterol descends to a definitely lower level.

With regard to alcohol there is little experimental evidence that alcoholics have more or less arteriosclerosis than non-alcoholics. When cholesterol and alcohol were given together, the blood cholesterol level was higher but neither the liver nor aorta showed arteriosclerotic lesions (Wertheim).[1] There is little evidence that the solvent action of alcohol on cholesterol aids in its diffusion or local concentration. It was noted by Ruffner (1921) that Mohammedan pilgrims who abstain from alcohol are relatively free of arteriosclerosis. Chronic alcoholics, who obtain a large portion of their daily caloric requirement from alcohol and therefore live on a relatively low diet, are remarkably free of aortic atheromatosis and arteriosclerosis.

Nicotine is known to cause coronary spasm and nicotine poisoning is without doubt a harmful factor. There is the tobacco angina, angina of effort which can be induced by smoking and the reduction of tolerance to exercise when the patient smokes one minute following exercise. Certainly the mass of clinical evidence, in so far as coronary disease is concerned, overwhelmingly favors the idea that chronic nicotine poisoning is conducive to atherosclerosis, especially coronary disease.[37,38] Occlusive vascular disease is definitely more prevalent in diabetics who smoke than in non-smokers. Smoking usually reduces peripheral blood flow, increases pulse rate and blood pressure. In a few cases, especially in the elderly, these changes are less. This may be just as true whether the nicotine effect on the heart and vessels is direct or indirect.

EXPERIMENTAL PRODUCTION OF TYPICAL ATHEROMAS

In the dog experimental production of typical atheromas is accomplished by the administration of large doses of cholesterol by mouth, more so if at the same time thiouracil is given. In such animals cholesterolemia may reach 800 to 2,000 mg. per cent.[1] Tween 80 and Triton A20, synthetic detergents given to rabbits intravenously, cause a striking increase in blood cholesterol and phospholipid levels. Alloxan diabetes produces lipemia, cholesterolemia and atherosclerosis. On the other hand, others have reported that in cholesterol-fed rabbits alloxan diabetes tends to reduce atherosclerosis.

Interesting studies have been made by Steiner and co-workers who found that rabbits fed 1 Gm. cholesterol three times per week consistently show atheromatous lesions after forty days; if, however, choline in 0.5 Gm. doses is given simultaneously, atherosclerosis does not make its appearance up to the eightieth day. Doses of 1 Gm. of choline delay the lesions to 90 or 100 days. Feeding choline to old hens caused a reduction of cholesterol in the blood, aorta and liver.[20] Inositol and methionine, according to Hermann and others, reduce blood cholesterol levels; soya lecithin and thiocyanate also reduce blood cholesterol levels.[29]

PROBLEMS FOR FUTURE RESEARCH

Numerous questions having more or less bearing on the etiology of arteriosclerosis await further clarification and answers. Among the basic questions are those relating to cholesterol and other lipids. What is the real significance of hypercholesterolemia? To what extent do restricted or semi-starvation diets influence hyperlipemia? Can an equilibrium be established between

ingested cholesterol or lipids, and cholesterol in the liver, brain, nervous system and the blood? Does the high incidence of arteriosclerosis in diabetes reflect a cholesterol imbalance in the diabetic? Pancreatic extract (lipocaic)[29] has been said to exert delaying effects on atherosis. Choline, inositol, methionine and soya lecithin have given favorable results in the restoration of normal cholesterol levels and possibly in the prevention of arteriosclerosis in experimental arteriosclerosis. Of what value are they in preventing, minimizing or abolishing atheromatous lesions? Is the cholesterol particle under certain conditions subject to physiochemical alterations which prepare it for an abnormal role and ultimately lead to deposition on the intima of the blood vessels. Moreton[7] put forth the theory that the cumulative effect of many fatty meals over a lifetime, producing showers of large lipid particles in the plasma, is an underlying cause of atherosclerosis in humans. These large particles pass with the lymph into the intima, inciting local reaction. Triglycerides and fatty acids are resorbed but cholesterol remains.

It is known that cholesterol occurs in all animal cells but is present in greater amounts in fat tissues, in the brain and in the spinal cord. Fat is a solvent and the vehicle for cholesterol, and rabbits fed cholesterol in oil seem to develop arteriosclerosis earlier than those fed crystalline cholesterol. Cholesterol is taken in with fatty foods but can also be formed in the body from fats, protein and carbohydrate; any compound which an animal can convert to acetate can be utilized to make cholesterol. Cholesterol is the mother substance of adrenocortical substance and sex hormones. It is a universal constituent of tissues but it is not a universal dietary constituent. It exists in invisible combination in cells and in colloidal suspension in the blood. Under polarized light cholesterin becomes visible as solid crystals and crystaline esters.

Our knowledge of cholesterol synthesis and metabolism in the body is still fragmentary. Isotope technics introduced by Schoenheimer, Rittenberg and Bloch will doubtless throw additional light on the role of cholesterol metabolism in vascular disease. Feeding experiments with deuterium-labelled cholesterol, followed by examining the isotope content of the liver, aorta, coronary vessels and blood plasma, open the possibility of estimating both exogenous and endogenous cholesterol that will mark a definite step forward. By feeding heavy water it was shown that half of the cholesterol hydrogen atoms have their origin in body water and that any compound which the animal can convert into acetate can be utilized in the synthesis of cholesterol by the liver. Neutral fats can be labelled with iodine^{131} and plasma fat curves established for the normal and abnormal. Cholesterol tracers open up the possibility of studying the role of cholesterol from the time of ingestion to its deposit in organs and tissues, and to its final decomposition and rate of each of these steps.

Another problem pertains to the mechanical effect of increased intravascular pressure as it exists in established hypertension. The mechanical factor is illustrated when an artery comes into contact with a bony surface, such as the misplaced subclavian artery in the case of a cervical rib; such an artery is more apt to become sclerotic than one imbedded in soft tissues. Another instance is that in poliomyelitis; when one leg or arm is involved, the blood vessels on the flaccid side show less sclerosis than those with normal muscle tone. In Ayerza's disease it is the hypertension in the pulmonary circuit which is primary and the arteriosclerosis secondary. To what extent hydrostatic pressure effect is actually responsible for the lodgment and diffusion of lipoid substance on and in the walls of blood vessels is not a settled question, although the concurrence of hypertension and arteriosclerosis is well known.

PROBLEMS AND PRINCIPLES OF TREATMENT

There are today new and interesting avenues of approach toward the possible

control of arteriosclerosis. Medical research, particularly in lower animals, indicates the possibility of arresting atherosclerotic processes and perhaps of reversion of processes already begun. We accept the fact that deposits of cholesterol in the intima of blood vessels occur in the early stages and the question is whether this occurs because of excessive amounts of cholesterol in the circulating blood or whether there is some alteration in the cholesterol molecule itself which under certain conditions initiates the lesion.

If excess cholesterol in the diabetic can be controlled or influenced favorably by the administration of insulin, will we do better from now on to use insulin more generously than we have in the past, at the same time avoiding hyperinsulinism? We have known for a long time that the large liver of young diabetics responds to generous doses of insulin. Does this imply that insulin improves liver function or fat metabolism or the restoration of a more normal enzyme and cholesterol metabolism, and ultimately may it delay or prevent arteriosclerosis?

Our approach to the treatment of arteriosclerosis, therefore, depends upon which viewpoints we accept as to its underlying causes and the relative importance of each. We can do nothing about the age of the patient but we may be able to do something about premature aging once we know how this depends on faulty nutrition. We can do little about hypertension until we know its origin and succeed in its control. We could do much, almost everything that might be necessary about diet control if only we knew just what should be done. If we admit that obesity is an underlying factor in atherosclerosis, and autopsy findings indicate that it occurs twice as frequently as in emaciated individuals, the necessary steps become clear to that extent. If the obesity is brought about by ingestion of excessive amounts of fatty foods, if the various fats and lipids act as vehicles for the diffusion of cholesterol throughout the circulatory system and if cholesterol, not readily metabolized, acts as a foreign substance and an irritant and destructive agent to the vessel wall, our method of approach again becomes clear, namely, avoidance of overeating and subsequent obesity, a strictly low-fat and low-cholesterol intake by which we may eliminate two or three possible underlying causes—obesity, hypertension and hypercholesterolemia. Strangely enough, this concept takes us back to Anitschikow[44] in 1913, the very beginning of the still prevailing viewpoint in our day.

If on the other hand cholesterol deposits in the intima and subintimal layers are of endogenous origin, if the lipoids there are elaborated within the arterial walls, control of these processes must be found in the darker recesses of the human metabolism. That would inevitably lead us into the fields of endocrine functions and enzyme activities, into the physiology and pathologic physiology of liver function and into still other even less known fields. Even that, it may be, is not entirely hopeless; for if we may trust our other experiences, by restricting fat intake to a minimum we would still be reducing the fat that feeds the fires of atherosclerosis.

A basic question today is, whether fat is a final storage form of excess food which can only be burned and converted to carbon dioxide and water, or is it part of the metabolic pool of the body to which fragments are being constantly added and from which they are continuously being withdrawn for various uses?

However all these questions may finally be answered, we in our day must care for our patients in the light of present day knowledge. That calls for a sensible middle-of-the-road plan in keeping with the present and future probabilities of good treatment. Today, as far as I can see, our plan should aim at restoration and maintenance of a normal or ideal body weight; for this we have adequate standards.[41] Our second aim is to allow our patients an adequate daily protein intake sufficient to prevent possible nitrogen deficit and hypoproteinemia, as may happen if we gave our patients less

than ⅔ Gm. protein per Kg. body weight. Our next aim must be to give the patient the smallest amount of fat that will make up a satisfactory diet; one which the sensible patient will not refuse and one toward which he will cooperate with his doctor. For the diabetic this may nearly always be achieved with 75 to 90 Gm. of fat per day and there is also a choice in the kinds of fat. Today we are recommending the use of vegetable fats to a large extent, aiming thereby to reduce cholesterol intake. Until the time comes when it is proved that it is futile to recommend low-fat and low-cholesterol diets we will continue to advise against excessive use of eggs, milk, butter, lard, sweetbreads, fat meats, etc., all of them known to be rich in cholesterol and high in fat content. We advise the use of oleomargarine to replace butter, and vegetable oils to replace animal fats for cooking; skimmed milk or buttermilk as a beverage and minimal amounts of other fat foods. According to our figures the cholesterol content of everyday foods is about as follows: 1 egg contains about 0.3 Gm.; 3 ounces of meat contain about 0.3 Gm.; milk contains about 0.2 Gm. per quart; 3 ounces of liver contain about 0.3 Gm.; 3 ounces of smooth muscle contain about 0.2 Gm. cholesterol.

Needless to say, we have no recognized specific medication against athero- or arteriosclerosis. The use of choline, methionine, inositol, soya lecithin, etc., is still in the experimental stage and the results thus far reported in animals and man will require much more controlled observation to justify general clinical use.

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Management of Diabetes in a General Medical Practice

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THE majority of patients with diabetes are and must of necessity be cared for by physicians who do not regard themselves as specialists in this field. It is with this group of physicians in mind that this article has been written, the purpose being to describe a practical and simplified program of diabetic management. The program avoids on the one hand excessively rigid control which may be time-consuming and costly, and on the other hand inadequate control which inevitably follows inattentiveness to the principles of satisfactory treatment. The treatment of diabetic emergencies, such as acidosis, is beyond the scope of this paper. I am concerned here primarily with the management of the diabetic patient who is ambulatory.

No time should be lost in establishing adequate control in any patient in whom more than minimal glycosuria has been demonstrated. Such a patient is to be considered a diabetic until or unless the glycosuria proves to be benign. The patient in whom glycosuria is more or less accidently discovered as a result of an office examination is not infrequently highly reluctant to enter the hospital and to assume what he is apt to regard as an unnecessary and unwarranted expense. The patient must be told that satisfactory treatment is based on accurate diagnosis. Fasting blood sugar determinations and (in borderline cases) glucose tolerance tests may be needed. The well equipped hospital will have facilities for laboratory investigation, not all of them likely to be available in the physician's office. The need for highly accurate laboratory procedures should be cited in urging hospital entry. There is a psychologic advantage in hospitalizing the diabetic patient shortly after his disease is discovered. If his physician regards his disease as serious enough to require hospital observation and instruction, the patient tends to be impressed by the potentially serious nature of his illness and is apt to receive his instruction in a more cooperative mood than might be attained in the physician's office. It is well for the patient to concentrate almost exclusively on the management of his diabetes during this introductory phase when a period of hospitalization will not seriously interfere for long with his usual work and activities. Getting him away from the well meaning but often ill advised sympathy of his friends and family is helpful. Finally, hospital instruction of the patient with the concentrated cooperation of the resident staff, nursing staff, dietetics department and the physician means an inestimable saving in time for both the patient and his doctor.

The patient is admitted to his room and instructed first in the collection of urine specimens for testing. A good routine involves testing a *freshly* voided urine specimen four times a day, before meals and at bedtime. The patient (and the nursing department) must thoroughly understand that a fresh specimen means urine which has been recently filtered through the glomeruli. The bladder must be emptied about half an hour before the test specimens are obtained in order that they may represent a fairly accurate index of the corresponding blood sugar values for the same time period, and contain a relatively small proportion, if any,

of "overflow glucose" spilled into the urine from a preceding meal. The nurses usually share the responsibility with the physician for teaching the patient to test his urine, using either qualitative Benedict's solution or the handier self-heating compressed testing tablets. Twenty-four hours after admission most patients test their own urine with only minimal supervision.

The diabetic patient deserves a painstakingly thorough physical examination with perhaps more than usual emphasis on the skin, mouth and odor of the breath (acetone); the height and weight; and examination of the ocular media and fundi. Not infrequently diabetes can be suspected from lens or retinal changes, and the physician who sees patients with diabetes will find his ophthalmoscope one of his most valuable aids. However, the physician's findings ought periodically to be checked against those of a competent ophthalmologist to be sure that development and progression of cataracts and diabetic retinopathy are not overlooked.

The size of the liver should be estimated by percussion and palpation. The status of the peripheral circulation especially in regard to presence or absence of pulsations in the arteries of the feet is of great importance. Evidence of diabetic neuropathy must be searched for. Reflex changes and absent or diminished vibration sensation in the lower extremities are particularly important as probable early manifestations of "diabetic neuritis."

Before breakfast on the morning after hospital admission blood is secured for determination of glucose and plasma cholesterol values, for hematologic examination, for a Wassermann test and sedimentation rate. A routine chest x-ray ought to be part of the initial examination. The need for other laboratory procedure such as the basal metabolic rate, other x-rays, such as those of the feet or pelvis for calcification of arteries, or of the stomach, gallbladder or colon, must be determined from the history and findings of the physical examination. If there is suspicion of chronic pancreatitis a flat plate of the region of the pancreas for evidence of calcinosis of the pancreas should be obtained before the roentgenologic study of the stomach, gallbladder or colon.

The diabetic customarily starts his dietary program with regimen containing 1,200 to 1,800 calories, which is to serve only as a temporary diet until a formula can be tailored to fit his needs. If, however, the fasting blood sugar level is found to be normal so that the diagnosis of diabetes mellitus is questionable and a glucose tolerance test is decided upon, the patient must be given a general diet with a generous proportion of carbohydrate for at least two days before the test is made. It will be remembered that a normal individual who has been subjected to a diet restricted in carbohydrates for as short a period as twenty-four hours or who has been subjected to prolonged fasting may show a diabetic response to a glucose tolerance test.

A fairly common oversight in the instruction of the diabetic patient in the dietary management of his disease is the apparent assumption that a patient who is in a hospital bed and who is satisfactorily controlled on say 1,800 calories with a small dosage of protamine insulin will do equally well when he is out of bed and actively at work. The error is serious because the patient gets hungry when he is working, has to eat more to feel comfortable and then is either bothered by a guilty conscience when he next sees his physician or avoids his next appointment entirely. This mistake can easily be avoided by carefully going over the patient's usual activities with him and basing the prescription for the dismissal diet on his probable daily energy expenditure.

Using either the Boothby and Berkson nomogram or a convenient slide rule, a forty year old male patient whose ideal weight is 160 pounds and who is 5 feet, 10 inches in height will be found to need 1,740 calories as his basal requirement (rest in bed or chair). For sedentary work 30 per cent should be added to this figure and for moderately heavy work 40 to 50 per cent.

If he is moderately active, he will need 2,450 calories; while on a day that he plays several sets of strenuous tennis or eighteen holes of golf, his need will increase to 2,600 calories or more.

When a diet order is written after the patient's admission to the hospital, it is well to make sure that this is not interpreted by the patient or by the dietitian as a discharge program. In general the patient will need an increased caloric intake of approximately 20 per cent over his hospital diet when he goes home, unless a weight reduction program is in order.

One drawback to the hospital instruction of the otherwise ambulatory diabetic lies in the enforced inactivity commonly associated with institutionalization. This can largely be avoided, the patient's insulin requirement lowered and his status more closely brought to approximate that of his daily home life if, after the first twenty-four to forty-eight hours, he is urged to get out of the hospital several times each day to take some moderate form of exercise such as a brisk half hour walk. In this way an artificial situation can be produced which roughly mimics his average daily activity at home and gives the physician a more secure basis for judging both dietary and insulin requirements than can be determined otherwise from hospital observation alone.

Once the patient's diet prescriptions have been written, the details of dietary management, food substitutions and the weighing or measuring of food portions may be safely entrusted to the hospital dietitian. She should be able to secure the complete cooperation of that member of the household who will be responsible for planning and cooking the meals. However, even though the patient does not actually perform the meal planning or cooking, he should be carefully instructed in the fundamentals of his diet to take care of situations in which meals are eaten away from home or in which he has to prepare his own meals.

The patient whose diabetes is severe enough to require insulin for adequate regulation is shown how to measure and regulate his dosage, and should be fully capable of continuing to administer his own insulin by the time he is ready to go home. Even those patients whose diabetes is adequately controlled by dietary restriction alone ought to have basic instruction in the administration of insulin to prepare them in case it should be needed at some future date. Such patients should have the experience of self-injection of a minimal and harmless dosage of 5 units or less of unmodified insulin taken just before a meal.

Approximately 50 per cent of one's diabetic patients will be capable of regulation without insulin. Another 25 to 30 per cent will require less than 30 units of insulin daily; this group is best handled on protamine insulin in one daily injection. The remaining group of diabetics, the so-called "Group IV," is apt to do poorly on protamine insulin alone. With dosages large enough to control day-time glycosuria night-time reactions are all too frequent. A smaller dosage of protamine-zinc insulin supplemented by unmodified insulin before each meal will give excellent control but leaves the patient with the unhappy prospect of giving himself three or four injections each day.

On the whole, this group of severer diabetics does best on a mixture of protamine and unmodified insulin taken one-half hour before the morning meal. The first day or two of diabetic regulation in the hospital will give valuable clues as to the probable magnitude of the patient's insulin needs so that by the second or third day one can switch to a mixed insulin dosage, changing the proportion and amounts of the two insulins depending upon the early morning and late afternoon urine tests. The principle of mixed insulin technics has been adequately and thoroughly discussed elsewhere.[1,2] For the majority of these diabetics a mixture containing a ratio of regular to protamine insulin of 2:1 seems to be most satisfactory, although the mixed insulin technic is sufficiently flexible to be adapted to almost any type of insulin

requirement, such as 1:1, 1½:1, 2:1, 3:1, and even 4 and 5:1. The development of new insulin currently designated NPH-50 and now on clinical trial[3] promises even simpler regulation for these severer diabetics. Many of the milder diabetics who do satisfactorily on a 2:1 insulin ratio (two parts of regular to one part of protamine insulin) also apparently are well controlled on globin insulin. I have used globin insulin satisfactorily in relatively few cases with excellent day-time control and reasonably good night-time control.

The patient using insulin must be carefully informed about insulin reactions: how to prevent them, how to recognize them and how to treat them. He must thoroughly understand that when the specimens of urine are continuously sugar-free for several days, the dose of insulin is to be reduced by at least 2 units. He must regard any unusual symptoms as possibly meaning the onset of a reaction, in particular any increased perspiration, any tremor or double vision. Finally, he must always carry sugar in some form on his person (loaf sugar is best) and must immediately take a loaf or two of sugar or the equivalent of this when symptoms of reaction—unusual perspiration with tremor and weakness—have developed.

The behavior of a person in a more severe reaction suggests inebriation; later coma supervenes. To avoid the embarrassment that this may occasion and to insure early treatment, every diabetic ought to carry on his person a card which gives the following information:

I have diabetes and my present condition may be owing to an overdose of insulin. Place sugar or candy in my mouth. If it fails to restore me in fifteen minutes, call my physician or send me to a hospital.
My name is_____
My physician is Dr._____
His address is_____
His telephone number is_____

The patient has now learned about his diabetes and his dietary requirements, he knows how to test his urine for sugar, he knows how to regulate and administer his insulin dosage, how to recognize insulin reactions and how to treat them. He has been in the hospital for a period varying from three days to a week and he is far better able to take care of himself than he was a few days previously. At this point he should realize that he is competent to manage his diabetes from 90 to 95 per cent of the time, barring the development of complications.

On his discharge from the hospital the patient should be instructed to test his urine before breakfast and before supper every single day. He is told to report to the physician for an office visit three to seven days later. This is partly to tie up any loose ends and to make sure that his instruction has been adequate and is thoroughly comprehended. Overlooked points will frequently turn up. At this visit the patient has the opportunity to go over his insulin dosage (if he is taking any) with the physician and to receive the assurance that he is administering the proper quantities of insulin if this is the case. The diet also is reviewed. If no serious difficulties are encountered, he can be discharged after this first office visit for a period of approximately three months with instructions to call the physician in the intervening period of time should any difficulties arise. When next seen, he is weighed, remeasured and his diet and insulin dosage evaluated in the light of his progress since leaving the hospital. In case he is getting too much or too little to eat, the services of the hospital dietitian may again be enlisted to help in working out a corrected dietary schedule.

If control is satisfactory the patient is given an appointment to return to the physician's office in approximately six months for a blood sugar determination. From then on he ought to be seen about twice yearly for help, encouragement, reexamination and instruction. If he is doing well, he ought to be told about it. If he is making mistakes, they should be corrected. Above all he should be continually en-

couraged to test his urine at least once a day, and if he is taking insulin, twice daily. The patient's carefully kept reports of his own urine tests are the most valuable contribution which he can make to his physician; they give far more information as to the progress of diabetic control than any number of blood sugar value determinations could do. Blood sugar determinations have been overworked and given an emphasis out of all proportion to their actual importance. They are expensive and often provide no information not already available from the results of simple qualitative urine sugar analyses. However, experience shows that the blood sugar determination serves as an inducement to maintain the continued interest of the patient in the proper management of his disease, and for this reason alone it should be made at intervals not less infrequent than once every three to six months. Furthermore, it has the function, not served by urinalyses, of detecting hypoglycemia, and not infrequently a patient overenthusiastic about keeping all his urine specimens completely sugar-free will increase his dosages of insulin above what is required, thereby inviting insulin reactions.

There are two extremes of mismanagement of the patient with diabetes. The first is the overcontrol method in which the patient is given a diet, a prescription for insulin and appointments to return to the doctor at much too frequent intervals for urine sugar or blood sugar determinations, until he soon becomes almost completely dependent on the physician for the entire management of his disease. The other is the undercontrol method in which the patient receives dietary and insulin instructions, starts out by carefully testing his urine and even counting calories, but because of the physician's lack of interest and his own understandable desire to lead as normal a life as possible and to think about his diabetes as little as possible, stops testing his urine for weeks and even months at a time, eats carelessly and takes insulin depending upon how he "feels." Sooner or later he becomes the patient whose only contact with the physician is during an illness, when he has a severe insulin reaction or when he is in acidosis. The wise physician will endeavor to set a course which carefully misses these extremes and will do his best to see that his patient avoids both overdependence and complete independence.

SUMMARY

1. A simplified method for managing the majority of diabetics seen in a general medical practice is outlined.

2. The importance of initial hospitalization for diagnosis, treatment and instruction is stressed. The few days spent in the hospital early in the course of the disease will mean an inestimable saving of time for both the patient and his physician.

3. The importance of daily or twice daily examinations for sugar of freshly voided urine specimens as indices of corresponding blood sugar values is re-emphasized.

4. Dietary instruction and insulin regulation are briefly discussed.

5. Follow-up management of the diabetic after his hospital discharge is described, and a plea is made for a program which avoids the extremes of excessively rigid control and of undercontrol.

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Diabetic Coma*

Metabolic Derangements and Principles for Corrective Therapy

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AMONG various complications of diabetes mellitus ketonemic acidosis and coma carry the most serious threat to the health and survival of the diabetic. The immediate hazards are evident; there is also increasing evidence that the late complications of degenerative cardiovascular disease are greatest among patients who have suffered numerous episodes of acidosis and coma.[1] Theoretically, such states should never develop in patients who are constantly alert in the observance of the few precautionary measures that are most essential. But when unexpected emergencies occur, the treatment of severe diabetic coma involves some of the most interesting and challenging problems in clinical medicine. Progressive stages in the development of diabetic coma are determined by a long series of closely interrelated functional derangements and chemical disturbances in the body, with secondary results that quickly become far more serious than the initial derangements of carbohydrate metabolism denoted by the name of the disease.

Like many other phases of diabetic management the treatment of coma has involved numerous conflicts of opinion among highly qualified authorities, sometimes leading to sharp exchanges of contradictions and reciprocal denunciations of various theories and practices followed in different centers. When closely examined some features of these conflicting views appear to be based upon argumentative distinctions without real differences in the fundamental concepts to which nearly all subscribe; attention is often confined to one or two or three points out of many known to be important in the chemical pathology of coma; and explanations of success or failure of treatment sometimes have been oversimplified by emphasis on the use and abuse of single items in the therapeutic armamentarium.

FUNCTIONAL DERANGEMENTS

In the development of diabetic acidosis and coma numerous factors are involved in a vicious circle of events in which all appear to aggravate the respective courses of separate but closely interrelated metabolic disturbances: (1) *Insulin insufficiency* or ineffectiveness; (2) *impaired glycogenesis*, increased glycogenolysis, hyperglycemia glycosuria, diuresis; (3) *increased hepatic ketogenesis*, ketonemia, ketonuria; (4) *metabolic acidosis*, with decreased bicarbonate and pH of the body fluids, and with hyperpnea a principal physical manifestation; (5) *increased cellular catabolism* liberating inorganic phosphates, potassium nitrogen and other metabolites from intracellular organic compounds; (6) *losses of electrolytes* by increased urinary excretion; decreased concentrations of electrolytes in extracellular and intracellular spaces; (7) *dehydration*, occurring primarily from losses of electrolytes, aggravated by loss of water through glucose-diuresis and by insensible loss of water through the lungs with the development of severe hyperpnea; hemoconcentration, diminished blood volume, falling blood pres-

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sure, shock, anuria; (8) *tissue damage*, resulting from increased cellular catabolism, anoxia and from release of "toxic" agents; (9) *coma*, resulting from ketonemic narcosis, cerebral anoxia, acidosis, etc.

These various factors are dealt with briefly in the following paragraphs as a basis for the subsequent discussion of treatment.

1. States of insulin deficiency may be defined as resulting from a lack of insulin, either endogenous or exogenous, or from circumstances leading to neutralization of the effects of available insulin. Ineffectiveness of insulin may result from the action of hormonal antagonists, specific antibodies, toxins or enzymes that destroy insulin, or of chemical conditions of the body fluids that inhibit enzymatic processes in which insulin is involved. It is obvious that many factors beyond a mere lack of insulin are operative in patients who require very large doses, sometimes huge, of exogenous insulin for the prevention of ketonemic acidosis or in the treatment of coma. Suggested causes of insulin resistance have been well reviewed elsewhere[2,3] and need not be considered here. Suffice it to say that the development of ketonemic acidosis is always initiated by insulin-insufficiency, regardless of the mechanism responsible for an increased need. In cases with treatment well established the occurrence of coma is usually clearly traceable to omission of the usual daily dose of insulin, to injudiciously decreased dosage or to failure to increase the usual daily dosage as needed during infections or illnesses that lead to increased insulin requirements.

2. Hyperglycemia may be regarded as incidental to disturbances in the hepatic regulation of blood sugar levels,[4] the result of decreased glycogenesis and increased glycogenolysis rather than a predominant disturbance of the ability of the tissues to burn sugar.[5] Hepatic glycogen probably represents only a small fraction of the total carbohydrate utilized in the body through various metabolic channels. Low concentrations of glycogen in the liver may be due to lack of or ineffectiveness of insulin to promote glycogenesis, to glycogenolytic effects of the adrenal, thyroid or pituitary hormones, to bacterial or viral toxins affecting the physical integrity of the liver cells and to starvation. Especially in children the element of starvation may be important in the depletion of glycogen reserves when there is failure of appetite, refusal of food or vomiting at the onset of infections. Varying degrees of hyperglycemia are not closely correlated with other severity indices of coma. Blood sugar levels may be very high in early stages of the development of a diabetic crisis and may fall considerably during coma (without insulin) presumably due to the exhaustion of carbohydrate stores in the whole body.

Hyperglycemia and glycosuria are concomitant factors leading to diuresis but *per se* are not critical in the chemical pathology of coma. Even extreme degrees of hyperglycemia in the absence of ketosis do not immediately lead to notable illness or functional disturbance other than diuresis although the latter may become intolerable to the patient.[6] Excessive excretion of electrolytes accompanies diuresis in diabetic acidosis; but glucose-diuresis of itself does not necessarily lead to salt deficits except under conditions of insulin-insufficiency. In studies on osmotic diuresis Rapoport and co-workers[7] recently demonstrated that when urine flow was greatly increased by loading with glucose (in non-acidotic diabetic patients receiving insulin), the excretion of Na and Cl tended to rise proportionately while that of K and P tended to remain constant. On the other hand, when an insufficient supply of insulin leads to increased cellular catabolism and release of intracellular components, an excessive loss of both intra- and extracellular electrolytes in the urine may be expected, regardless of the degree of diuresis.

3. Abnormally rapid hepatic ketogenesis is associated with increased glycogenolysis and decreased concentrations of glycogen in the liver. Mutually aggravating factors are operative, inasmuch as glycogenolysis is increased by the state of ketonemic acido-

sis. The theory of overproduction of ketone bodies in diabetic acidosis is now well accepted, with the establishment of evidence that the usual rate of utilization of ketones by muscles and other extrahepatic tissues is unimpaired in depancreatized animals.[8–10] Ketonemia increases rapidly when overproduction exceeds both the capacity of the kidneys for secretion and the rate of utilization of the ketone bodies by muscles and other peripheral tissues.[11]

4. Metabolic acidosis, characterized by low bicarbonate and low pH of the blood plasma, results partly from the accumulation of ketones and other acid metabolites, partly from losses of mineral cations that are excreted with ketone acids, phosphates and other anions in the urine; also, relative hyperchloremia often co-exists with a lowered concentration of sodium in the plasma, especially in later stages of increasing hemoconcentration. The state of acidosis *per se* aggravates the course of the metabolic disturbances by multiple effects, directly or indirectly interfering with the action of insulin and generally accelerating catabolic processes in all tissues; e.g., lowered pH of the fluids inhibits synthesis and accelerates the decomposition of intracellular phosphorylated compounds that are involved in the carbohydrate cycle. The hyperpnea that accompanies acidosis involves severe muscular effort, imposing burdens of fatigue and anxiety, and contributes to the development of dehydration, especially in late stages, by increasing the loss of water vapor in expired air. Correlating hyperpnea in acidotic patients with changes in blood pH, Kety et al.[12] observed respirations increasing sharply below a threshold at around pH 7.2 to a maximum in the region of pH 7.0 but decreasing with lower values as the severity of acidosis increased, probably owing to depression of the medullary centers.

5. Increased tissue catabolism in the diabetic crisis involves the liberation of inorganic phosphates and associated cations (especially potassium) from cells into the plasma whence they are excreted in the urine unless renal function is impaired. Metabolic balance studies have furnished abundant data on the nature of the metabolic losses that occur in diabetic acidosis. Von Noorden in 1905 stressed the importance of phosphaturia in diabetic coma as an index of cellular catabolism. The classic study by Atchley, Loeb et al.[13] demonstrated that losses of K and P were higher in proportion to N than the ratio found in tissues, indicating that labile intracellular compounds were lost without necessarily a complete cellular breakdown.

Insulin deprivation leads to an increase in basal metabolic rate and to increased glycogenolysis before acidosis is apparent. With the development of acidosis the low pH of the body fluids favors the enzymatic decomposition of labile organic phosphates in the cells. When the rate of breakdown exceeds the rate of phosphorylation and resynthesis of compounds involved in the glycolytic cycle, inorganic phosphates are liberated into the blood. Increased phosphaturia in states of acidosis has been commonly explained as a renal mechanism for conserving cations, for maintaining the alkali reserve in the plasma, diminished tubular reabsorption of phosphates occurring as an effect of lowered pH on the kidney.[14] Increased liberation of inorganic phosphates from tissues is probably primary and the more important factor in phosphaturia.

6 and 7. Dehydration in diabetic acidosis results primarily from loss of electrolytes as it does in other conditions in which salt depletion leads to diminished ability of the body to retain water. Data from metabolic studies indicate that the losses are primarily cellular, depletion of extracellular elements occurring as a concomitant or secondary effect. In later stages vomiting (or the accumulation of fluid in a dilated stomach without actual vomiting) may aggravate the loss of extracellular electrolytes, chloride and sodium. The progressive manifestations of dehydration with depletion of total body fluids, hemoconcentration, diminished circulating blood volume, lowered blood

pressure and shock, are well known and need not be discussed here. The time element is important in determining the course of the depletion of the body fluids. When the evolution of acidosis and coma is rapid, dehydration may be less pronounced than when acidosis exists several days before the onset of coma and there is time for a greater total loss of electrolytes. Hypoelectrolytemia is found during the development of acidosis while polyuria and polydipsia are concomitant symptoms but the picture may change considerably in later stages when polydipsia ceases with loss of consciousness or vomiting interrupts the intake of water. At this time, rising levels of non-protein nitrogen may indicate inadequate renal function due mainly to a lack of water. In the stages of coma when hyperventilation is increasing and fever accelerates the rate of water loss by vaporization, the loss of water alone from the lungs in expired air and through the skin in insensible perspiration becomes an increasingly important factor aggravating the state of dehydration. Such water loss leads to hemoconcentration in the true sense, with increasing osmolarity of the plasma. This sequence of events is similar to that leading to plasma hyperosmolarity and hyperelectrolytemia in infants with gastrointestinal disease complicated by hyperventilation.[15] Diarrheal disease ordinarily leads to dehydration from salt loss, characterized by hypoelectrolytemia, but with severe hyperventilation provoked by co-existent respiratory tract infection the picture may change rapidly to one of hemoconcentration from water loss, with extreme degrees of hyperelectrolytemia and hyperosmolarity of the blood plasma. Similar conditions may be found occasionally in diabetic coma. For example, in an infant, three months of age, suffering a respiratory tract infection and fever, with severe hyperpnea, probably acidotic more than forty-eight hours before the diagnosis of diabetes was made and treatment was started, the concentrations of total base and of Cl in the blood serum were 180 and 135 m.Eq./L., respectively.

8. A concept of irreversible tissue damage is generally offered to explain the high mortality that is universally found among comatose patients, rising sharply with the duration of coma regardless of treatment.[16-20] It is generally agreed that chemical analyses of the blood of patients before the start of treatment show little difference between those who recover from coma of short duration and those who have been comatose a long time who do not recover. Investigators have turned their attention increasingly to the cells, rather than extracellular fluids, seeking explanations for the damage that is associated with various indices of severity of coma. Damage to vital organs may be ascribed to factors of increased catabolism induced by acidosis, involving the liberation of phosphates and mineral ions as already mentioned, to specific histotoxic effects of ketone bodies, especially acetoacetic acid, and to interference with oxygen exchanges leading to tissue anoxia. The last item now appears to be the most important. In studies done on fourteen patients in severe coma, with mortality 43 per cent, Kety and co-workers[12] found that the measurement of cerebral oxygen consumption was the only one of many tests performed before or at the start of treatment that seemed to have prognostic significance. They report that in these patients "there seemed to be a critical level for cerebral oxygen utilization of 2.1 cc. per 100 Gm. of brain per minute at or below which consciousness disappeared, compared with a consumption of 3.3 cc. per 100 Gm. per minute found in mentally alert normal subjects." With but one exception a cerebral oxygen consumption below that critical level appeared to be incompatible with survival.

Acute functional disturbances of the heart and kidneys may be ascribed similarly to the effects of acidosis and of cellular anoxia attending a diminution in circulating blood volume, hemoconcentration and shock. In older persons there are usually the complications of already existent cardiovascular disease. Specific effects of changes in the

concentration of potassium in the blood plasma on myocardial function, in severe coma and in the postacidotic period have been revealed by electrocardiographic studies.[21]

9. Coma, the ultimate and most critical manifestation of the diabetic crisis, is the most important of clinical indices correlated with prognosis. In their extensive study of blood gases, electrolytes and cerebral blood flow in diabetic subjects, mentioned above, Kety and co-workers found a close correlation between mental states (normal, alert, confused, unconscious) and the rate of utilization of oxygen by the brain; also, there was a good correlation between mental state, depression of cerebral metabolism and rising levels of blood ketones. Coma was associated with a 40 per cent reduction in cerebral utilization of oxygen in spite of an augmented rate of cerebral blood flow and normal arterial oxygen saturation. Kety et al. concluded that the observed depression in cerebral metabolism could be ascribed both to the state of acidosis *per se* and to ketone substances probably acting as histotoxic agents.

RECOVERY

The steps involved in recovery from diabetic coma may be described as a reversal of those that characterize the development of acidosis. Again, numerous factors of metabolic adjustments are closely interrelated and mutually dependent upon the effects of various therapeutic measures: the administration of insulin and parenteral fluids, and realimentation.

Effective doses of insulin promote glycogenesis, inhibit glycogenolysis and hepatic ketogenesis and reduce tissue catabolism. The action of insulin is dependent upon available supplies of substrates for enzymatic reactions, e.g., sugar, phosphorus and potassium, and upon the influence of pH on the enzymatic transformations; perhaps also upon amounts of enzymes and coenzymes in the tissues. Insulin may promote processes of phosphorylation in extrahepatic tissues in ways not yet well understood, not entirely linked with its blood-sugar-lowering effects or the transfer of sugar from plasma to cells.[22,23a,b] Ketone bodies are eliminated partly by renal excretion, more by utilization in extrahepatic tissues.[7,11] The replacement of ketone anions by bicarbonate is accompanied by restoration of normal pH values and by simultaneous shifts in the distribution of Cl, Na and other elements in extracellular and intracellular fluids. Parenteral fluid therapy is directed to the restoration of a normal circulating blood volume, replacement of electrolyte losses and rehydration of the whole body, essential to all phases of functional recovery. Processes of glycogen formation and re-establishment of normal carbohydrate metabolism in tissue cells involve the uptake of phosphorus and potassium from extracellular fluids. Concomitantly with recovery from acidosis, with rise of plasma pH to normal, the excessive urinary excretion of phosphate, potassium and other waste metabolites is sharply reduced; phosphaturia may be practically nil for several days after symptomatic recovery. The diminished phosphaturia is explained as the result of (1) changes in tubular reabsorption of P found with changes of pH in the blood, (2) diminished liberation of inorganic phosphates from cells as tissue catabolism is reduced and (3) lowered concentrations of inorganic P in the plasma. Metabolic equilibrium is reached *after* a normal nutritional state is restored by realimentation.

BLOOD CHEMISTRY

At each stage of development of acidosis and recovery the chemical state of the blood is the resultant of all processes that influence its changes. The composition of the plasma for the most part does not give an accurate indication of cellular changes. The direction and rate of chemical changes in the plasma, if determined by serial measurements at short intervals, would offer better indices of the physiologic state of the whole body than any static representation of the composition of plasma, e.g., as in diagrams depicting electrolyte structure of the plasma

at a given moment. Just as blood sugar levels depend upon rates of glycogenesis, glycogenolysis, gluconeogenesis, utilization and excretion of glucose, so the concentrations of inorganic P and K in the blood plasma depend upon the rate and direction of exchanges of these elements between the cells and plasma, and the rates of their excretion in the urine. The levels of inorganic P, K and non-protein nitrogen in the plasma usually remain normal or low during the early stages of the development of acidosis when urinary excretion of these elements is steadily increasing but their levels rise rapidly in later stages as the result of increasing cellular catabolism plus failure of renal function to "clear" the plasma. In severe coma concentrations of inorganic P and K in the plasma may be and usually are high despite an increasing deficit of these elements in the blood and other tissue cells.* With increasing acidosis Cl and Na ions enter the cellular phase as P and K leave the cells. The ratio of cellular chloride to serum chloride, a function of pH, offers an index of shifts in the distribution of Cl between cells and extracellular fluids in the whole body. It is to be noted that this ratio is relatively high in acidosis regardless of whether the concentration of Cl in the plasma be low or high. Some investigators have found elevated concentrations of pyruvic acid in the blood plasma a sign of cellular disturbances in which the coenzyme cocarboxylase (thiamine pyrophosphate), required for the metabolism of pyruvic acid through the Krebs cycle, may be inactivated or lost with other phosphorylated compounds.[24a] During recovery when resynthesis of intracellular compounds involves a rapid uptake of P and K from the plasma, hypophosphatemia and hypopotassemia (with reference to plasma) indicate something of the rate and direction of exchanges occurring between cells and plasma, not the degree of deficiency of those elements in the body at a given time.

* As commonly used, the words hyperphosphatemia and hyperpotassemia apply only to plasma concentrations.

The organic acid-soluble phosphorus compounds of the blood cells constitute a labile store of phosphorus serving diverse functions in the body.[25] In constant state of flux, synthesized and decomposed through reactions of the glycolytic enzyme system, the phosphoric esters act as transport substances, participating in carbohydrate metabolism and in the transfer of phosphorus for various metabolic purposes; and as intracellular anions they play an important role in the ionic equilibrium of the blood. Although the total amount of phosphorus thus carried in the cells of the blood is small compared with the total labile stores of phosphorus in the body, the changes found in the red cells in different pathologic conditions offer a valuable index of the *state* of the stores of related labile compounds in other tissues. In diabetic coma there is always a profound reduction in concentration of the phosphoric esters in the red blood cells. During the development of and recovery from the acidotic state the direction and rate of changes in the organic phosphates in the blood cells give clues to the probable sequence of closely related chemical changes taking place in other tissues which are less easily studied than the blood.

The total organic acid-soluble phosphorus (OASP) of the red cells, normally around 50 to 60 mg. per 100 cc. of packed cells, is made up of approximately 10 mg. adenosinetriphosphate, 15 mg. hexosephosphates and 25 to 35 mg. diphosphoglycerate. These phosphoric esters normally constitute a considerable part of the intracellular anions. Expressed in milliequivalents per liter of water, in packed cells, the total average concentration of anions, 175 m.Eq., is comprised of HCO_3 17, Cl 74, inorganic phosphate 1, organic phosphates 45 (of which the diphosphoglycerate represents about 30 m.Eq.), hemoglobin 33, and undetermined anion equivalents 5 m.Eq., estimated by difference. These anions are matched by the cations Na 22, K 144 and Mg 8 m.Eq. per L. of water. The phosphoric esters and hemoglobin together thus comprise about 78 m.Eq. of non-diffusible

anions, which influence the distribution of diffusible ions (Cl and HCO_3) between the cells and plasma according to principles of the Donnan equilibrium.[26] In various conditions in which large changes in concentration of Cl in the blood occur, a reciprocal relationship has been observed between the concentrations of organic phosphates and of chloride in the cells comparable to that found between Cl and HCO_3 in the plasma; e.g., high cellular chloride with low concentrations of organic phosphates in ammonium chloride acidosis and in diabetic acidosis and, conversely, low cellular chloride with high concentrations of organic phosphates following pyloric obstruction, and in nephritis with hyperphosphatemia.[27]

All changes in concentration of the phosphoric esters necessarily hinge upon the enzymatic reactions of phosphorylation and dephosphorylation in the glycolytic cycle. Inorganic P enters this cycle in the phosphorylation of adenylic acid, with the formation of adenosinetriphosphate (ATP), and leaves the cycle when liberated from ATP after various intermediate steps of transferal in the formation and decomposition of hexosephosphate, diphosphoglycerate and other intermediate compounds. Principal factors influencing these transformations are changes in pH and in amounts of substrates available. By experiments *in vitro* it has been shown that pH values of 7.4 and above favor synthesis while values below 7.3 favor decomposition of the phosphoric esters and liberation of inorganic P from the cells.[28] Presumably the same effects of changes in pH are operative in conditions of severe diabetic acidosis and recovery: lowered pH leading to decomposition of intracellular organic phosphates and to excessive phosphaturia as long as renal function is adequate to clear the plasma of liberated inorganic phosphates; and normal pH values (after correction of acidosis) favoring the restoration of the organic phosphates.

Following the withdrawal of insulin in diabetic subjects who are prone to develop acidosis easily the concentration of phosphoric esters in the blood cells decreases rapidly with the development of ketoacidosis. If the duration of acidosis has been brief, resumption of insulin injections is followed by prompt restoration of the organic phosphates within a few hours, with correction of the state of acidosis and elimination of ketosis. The time relationships of such changes parallel closely those of the urinary losses of phosphorus and potassium that have been demonstrated during the development of acidosis and the retentions of P and K during recovery (Atchley, Loeb et al.[13]; Butler et al.[29] and others). That the state of acidosis *per se* is responsible for these changes is indicated by the fact that a similar sequence of changes may be observed in ammonium chloride acidosis: extreme phosphaturia accompanying a great decrease in concentration of organic phosphates in the blood cells during periods of administration of NH_4Cl; cessation of phosphaturia and recovery of normal concentration of OASP in the blood cells when the NH_4Cl is stopped.[27] When phosphate losses have been large with prolonged acidosis in cases of severe coma, the restoration of organic phosphates in the blood cells is slow during recovery, lagging considerably (even for several days) behind the correction of ionic equilibrium in the plasma and clinical signs of recovery.[30,31]

The transfer of mineral cations between cells and plasma is closely linked with the enzymatic reactions of phosphorylation. Changes in the concentration of organic phosphates and of K in the blood cells during the development of and recovery from diabetic acidosis are closely parallel, probably dependent upon common factors: low cellular concentrations of organic phosphates and K resulting from decomposition of the phosphoric esters in the acidotic state and from lack of substrate (either P or K or both) for their resynthesis in the recovery period.

The observations made on changes in the distribution of phosphorus compounds in the plasma and cells of the blood, correlated with data from metabolic balance studies,

afford a basis for the concept of two phases of altered mineral metabolism during the development of and recovery from diabetic acidosis: a phase of acidosis and dehydration, during which losses of both extracellular and intracellular ions and fluids occur: and a post-acidotic phase during which, with restoration of anabolic cellular functions, the avid uptake of intracellular ions by tissue cells results in a depletion of these ions in the extracellular fluids. Subnormal levels of inorganic P and K in the plasma in the recovery period may be ascribed to this uptake by the cells rather than to urinary excretion at that time as some have suggested.

Hypophosphatemia, characteristic of the recovery period, is not attended with recognized functional disturbances, but severe depletion of serum potassium results in the now familiar syndrome of hypopotassemia, as described by Holler[32] and others:[33,34] generalized muscular weakness, paralysis of respiratory muscles and cardiovascular difficulties attended with characteristic changes in the electrocardiogram. Hypophosphatemia and hypopotassemia are but two features of a series of postacidotic metabolic readjustments which may also involve Ca and Mg.[35] Under other conditions and in subjects with different nutritional backgrounds postacidotic readjustments may lead to manifestations of other deficiencies: e.g., tetany as a manifestation of hypocalcemia in the postacidotic period after diarrheal disease in infants.[36]

THERAPY

In debates over various schemes for the treatment of coma many writers have rightly expressed fears of the harm that can be done by abuses of practically all of the commonly employed procedures. Examples have been cited of deaths that followed the administration of excessive amounts of glucose solution, alkali, salt solutions and even of insulin. Usually these reports lack clear evidence that deaths were in fact due to the procedure indicted and they do not constitute valid arguments against a more judicious use of any of these valuable procedures. In many instances it could be claimed that the deaths were due to neglect of supportive therapy rather than to the specific abuses: e.g., failure to correct rapidly increasing acidosis by judicious administration of alkali; use of hypertonic glucose solution alone in large amounts without adequate salt replacement; use of large doses of sodium bicarbonate without adequate treatment with other fluids. Some deaths in the postacidotic period have been due to hypopotassemia, a phenomenon only recently appreciated.

Primary objectives in the treatment of coma should be the restoration in the body of *optimal conditions for functional recovery*, as well as the supply of materials needed for the restoration of normal chemical structure of the tissues and fluids. Rules for the treatment of coma, to be helpful, must be flexible, permitting changes of procedure in individual cases according to the dictates of clinical judgment in evaluating the state of each patient, the severity and duration of acidosis, coma, hyperpnea and dehydration, evidences of recent loss of weight, the state of the blood-circulation and the presence of infection. Therapeutic procedures should be employed with attention to interrelationships existing among their separate effects. If treatment is started early in the development of the crisis, when ketonemic acidosis has been of short duration, the administration of insulin alone or with moderate amounts of salt solution may be sufficient to promote rapid recovery. Then the re-establishment of normal fluid and electrolyte equilibrium follows natural processes of realimentation. Fairly simple schemes of treatment[37] have led to good results even with severely comatose patients. Under critical conditions, however, the use of all available procedures for corrective therapy and of laboratory studies for their control should be carefully considered.

The following schedule for the treatment of coma is offered tentatively as a basis for further discussion of guiding principles and of current opinions that are held in different

centers regarding the use of the respective procedures.

I. Insulin may be administered in most cases in moderate doses (30 to 60 units per hour in adults, 10 to 20 units in small children) given in divided doses at short intervals, fifteen to sixty minutes, to assure a continuous supply and an overlapping of the effects of each dose. In unusual cases of insulin resistance larger doses will be required.

II. Parenteral fluid therapy, comprising the administration of water, electrolytes, glucose, blood: (1) *physiologic salt* solutions given intravenously first (mixed with alkali as indicated), in amounts approximating 1 to 2 per cent of the body weight per hour during the first two or three hours, then more slowly; (2) *alkali*, as sodium bicarbonate or sodium lactate, given with the first intravenous fluids, as soon as the degree of acidosis is known, in amounts sufficient to bring the plasma pH to normal or to raise the plasma bicarbonate to around 13 m.Eq. per L., or 30 volumes per cent; (3) *glucose*, administered as 5 per cent solution in physiologic saline solution or in water, after the third to sixth hour of treatment, after the correction of acidosis with alkali and when the effectiveness of insulin is assured but without waiting for the blood sugar to fall to normal or hypoglycemic levels; (4) *potassium and phosphate salts*, administered cautiously intravenously or by mouth, after four to six hours, four doses of KCl, 1 Gm. each, hourly, anticipating hypopotassemia and cellular needs for replenishment in cases where severe depletion is suspected or known; (5) *whole blood or plasma transfusions*, indicated in cases with anemia, persistent circulatory collapse and shock, anuria.

III. Vitamin preparations, especially of the B-complex, given in parenteral fluids and with oral realimentation.

IV. Chemotherapy, started promptly in the presence of infections.

V. Feeding by mouth should be started as early as possible, as soon as vomiting has ceased.

PROCEDURES

Insulin. There is unanimous agreement that insulin should be administered at once when the diagnosis of diabetic acidosis is made. But opinions differ widely on the dosage that should be employed during the first hours of treatment, as well as on the use of supportive treatment which may influence the effectiveness of insulin. Root and co-workers[38] recommend high initial doses of insulin, usually 100 units, with 300 or 500 units extra if the blood sugar is above 600 or 1000 mg. per 100 cc., to be followed by repeated doses at intervals depending on the results of clinical and laboratory tests. Among recommendations for the routine use of high doses perhaps the most extreme is that of Micks[39] who, claiming to follow Root's teaching, recommended an initial dose of 100 units for patients in pre-coma, 500 units for patients in true coma, followed by 100 units given (intravenously) every fifteen minutes until the appearance of clinical signs of improvement. Mick's scheme is like Root's in that the administration of insulin is accompanied only by intravenous perfusion of salt solution (4 to 6 L.) in the first few hours, with no glucose "until the blood sugar is low," and with no alkali used to correct the acidosis. This article elicited an editorial in the same journal[40] calling attention to the dangers from hypoglycemia likely to be incurred by such a procedure, also a note by Lawrence[41] expressing objections and citing his own satisfactory experiences in treating patients "in severe pre-coma" with total dosage of 124 to 196 units in divided doses during sixteen to twenty-four hours.

Dangers of damage to the central nervous system by the effects of large doses of insulin must be borne in mind; although those who recommend large doses in the treatment of coma generally discount this possibility, trusting that the administration of glucose will arrest the progress of any deleterious reactions. Yannet[42,43] found that large doses of insulin in cats led to demonstrable damage to the brain, with loss of potassium.

This effect was only partly attributable to hypoglycemia *per se* as larger doses produced more damage without notable differences in the degree or duration of hypoglycemia.

Overdosage with insulin may have other unfavorable effects not entirely disclosed by blood sugar levels. Somogyi[44] has pointed out that there are two phases in the action of insulin when given in a dosage sufficient to provoke hypoglycemia. In the first, excessive ketogenesis is arrested as liver glycogen increases and glycogenolysis is inhibited; in the second, with hypoglycemia, ketone formation increases as liver glycogen is again depleted by increased glycogenolysis. Thus during recovery from coma, after the elimination of ketosis there may be a "paradoxical" reappearance of ketonuria dependent upon the development of hypoglycemia. While such ketonuria is usually mild, secondary effects may be important. Mobilization of liver glycogen involves the liberation of potassium to plasma[45] which may add to the instability of potassium metabolism in this critical period of recovery.

Haste in the administration of very large doses of insulin merely to reduce the blood sugar quickly seems futile, considering the fact that varying degrees of hyperglycemia cannot be correlated with the severity of acidosis or the depth of narcosis in comatose patients. Maximum effectiveness of insulin in the reduction of ketosis may depend more upon supportive measures than upon the speed with which the blood sugar level is reduced.

Parenteral Fluids. Intravenous therapy is directed primarily to the correction of abnormalities in the extracellular fluids and to secure improvement in the circulating blood volume, secondarily to promote intracellular processes of recovery. There seems to be no valid reason for the use of the subcutaneous route for the administration of fluids except difficulty in venipuncture, and this difficulty should be rare. Fluid under the skin serves no useful purpose until it is absorbed into the circulation, and absorption is slowest in the patients with poorest circulation in whom the immediate need for fluids to improve the blood volume is most urgent. In the regulation of dosage a working rule followed in our pediatric service is that the total volume of all fluids administered parenterally in the first eighteen to twenty-four hours of treatment may amount to between 10 and 15 per cent of the body weight, but with intravenous perfusion at the rate of 1 to 2 per cent of the body weight per hour during the first two or three hours. Intravenous perfusions should be discontinued promptly when the urine becomes ketone-free or nearly so and when fluids are taken well by mouth, trusting natural processes of realimentation to complete the restoration of metabolic equilibrium.

Salt Solutions. Practically all schemes for parenteral fluid therapy provide first for generous amounts of physiologic salt solution, usually 2 to 4 L. in adults, administered rapidly in the first few hours to cover primary extracellular needs for rehydration and continued at a slower rate in combination with glucose or with other salts.

Alkali. There are widely divergent differences of opinion on the advisability of administering sodium bicarbonate or sodium lactate for the correction of acidosis in the treatment of coma. Among those who object, some merely maintain that such therapy is unnecessary since the gradual elimination of ketosis by insulin leads to an increase of plasma bicarbonate without the addition of sodium. Others insist that it is potentially dangerous, citing cases in which the administration of alkali to raise the plasma bicarbonate from acidotic levels to normal was followed by states of severe alkalosis later in the recovery period; or, worse, cases in which severe alkalosis was induced when large doses of sodium bicarbonate were employed to "treat" acetonuria under the mistaken idea that acetonuria necessarily means acidosis. But, as many others have pointed out, the fact that overdosage of a drug can be harmful is not a contraindication to its more judicious use to secure a desired effect. Arguments favoring rapid correction of acidosis by the administration of alkali in one form or another may

be based on evidence, already discussed, that low plasma pH values are associated with increased tissue catabolism, breakdown of intracellular phosphorus compounds and losses of P and K in the urine. A recent report[46] of metabolic studies on diabetic subjects in severe acidosis and during recovery, treated with insulin, saline and glucose solutions, states that "*potassium continued to pour out of cells throughout these earlier hours of therapy.*" Losses of P and K in the urine that continue during the early hours of treatment may be ascribed to uncorrected acidosis. As early as 1922 Campbell[47] maintained that the administration of sodium bicarbonate in combination with the newly developed insulin therapy was desirable because it accelerated recovery from severe acidosis.

There is reason to believe that the action of insulin in the treatment of coma is inhibited by conditions of ketonemic acidosis and is favored by the administration of alkali. Kirk[48] described two cases of coma precipitated by infection and omission of insulin in which there was failure of response to initial doses of insulin. Admitted to the hospital in a pre-comatose state, drowsy but conscious, both patients rapidly became more comatose and more acidotic after the start of treatment with insulin and intravenous perfusion of salt solution. The administration of sodium bicarbonate solution was followed immediately by recovery of consciousness and by symptomatic improvement before more insulin was given. Both patients responded normally to subsequent moderate doses of insulin.

A report by Shephard[49] offers an interesting comparison with the one just cited. Shephard reported a case of severe coma, with treatment guided by Mick's recommendations,[39] in which 56,000 units of insulin were administered in twenty-six hours. A thirty-two year old man, previously taking 42 units of insulin a day, abruptly went into acidosis and coma when, with a cold, he did not eat and omitted his insulin. Deeply comatose when admitted to the hospital he failed to respond to 1,000 units of insulin given in the first ten hours. Progressively larger doses were given, to a total of 56,080 units in twenty-six hours, after which time the blood sugar fell to 24 mg. per 100 cc. and he developed convulsions. Recovery followed the administration of glucose. The patient was discharged after a few days, again receiving only a moderate dosage of insulin for daily control. It seems likely (to this reviewer) that in this case the existing conditions of severe acidosis could account for the ineffectiveness of the insulin and that correction of the acidosis with alkali might have favored earlier effectiveness of the insulin.

Conditions of keto-acidosis may interfere with metabolic readjustments that are set in play by insulin apart from its blood-sugar-lowering effects. A report by Hedon[50] in 1927 describing dramatic effects of the administration of sodium bicarbonate to a diabetic dog in severe acidosis and coma is especially interesting in this connection. The dog had been maintained in good condition by injections of insulin for thirteen months after pancreatectomy. When insulin was withheld, the animal quickly developed intense glycosuria, polyuria, thirst, loss of weight, increasing ketosis and went into complete coma on the fifth day. Injections of insulin failed to revive the dog. After several hours acidosis was apparently increasing (blood CO_2 decreased to 11 volumes per cent) and the dog appeared moribund although the hyperglycemia was reduced and glycosuria ceased. Intravenous injections of sodium bicarbonate solution were followed within a short time by signs of revival. After four hours when the blood CO_2 had risen to 35 volumes per cent, the dog walked across the laboratory in search of food. With continuation of the usual injections of insulin complete recovery followed.

More compelling arguments for the use of alkali may be found in the report by Kety et al.[12] that in comatose patients lowered pH of the blood was closely correlated with depression of cerebral oxygen metabolism, which proved to be an im-

portant prognostic index of mortality. These investigators demonstrated that the arterial blood pH in comatose patients could be brought quickly to normal by intravenously injected doses of sodium bicarbonate just sufficient to raise the blood CO_2 content by only 10 or 15 volumes per cent. They point out that since large doses are not necessary to bring the pH to normal, much of the objection against the intravenous use of alkalis in the treatment of coma can be met.

If the factor of acidosis, lowered pH of the body fluids, is recognized as a critical one in tissue damage that increases with the duration of coma, its *early* correction appears to be one of the most important steps in rational therapy. But when correction of acidosis is practised, dosage should be carefully controlled. Continuous administration of alkalizing solutions (e.g., mixtures of sodium chloride and sodium lactate) has not infrequently led to the development of alkalosis and edema during the recovery period. Formulas employed for the calculation of dosage of alkali[51] are based principally on that of Van Slyke,[52] assuming that administered sodium bicarbonate will be distributed in fluids constituting 0.7 L. for each Kg. of body weight. Although the use of this formula (essentially empiric in derivation) has been criticized on theoretic grounds,[29] it proves an extremely valuable aid for estimating amounts of alkali required to correct acidosis to within a range selected as desirable in a given case and to avoid overdosage. In our hospital we use the following formulas for estimating amounts of sodium bicarbonate (preferred) or sodium lactate required *to raise the plasma CO_2 content to between 10 and 15 m.Eq. per L., or to between 20 and 30 volumes per cent:*

1. To raise the plasma CO_2 content 1 m.Eq./L., give 0.058 Gm. of $NaHCO_3$ or 4.2 cc. of M/6 Na-lactate solution, per Kg. of body weight.
2. To raise the plasma CO_2 1 volume per cent, give 0.026 Gm. $NaHCO_3$ or 1.8 cc. of M/6 Na-lactate per Kg. of body weight.

Glucose. Current discussions on the use of glucose in the treatment of coma are mainly concerned with the time at which its intravenous administration should be started. All authorities agree that glucose should be administered after the first four to six hours when the blood sugar is falling to normal levels or below, although there is less agreement as to the amounts and manner of its administration after that time. Only a few pertinent points in the controversies that have been waged on this subject in the past need be recalled here.

Objections to the early administration of glucose have been based principally on claims that at hyperglycemic levels glucose is toxic, it injures islet cells of the pancreas, causes hepatic and renal damage, has been a precipitating cause of coma and neutralizes insulin action. Some of the arguments offered in favor of the early administration of glucose are: that prior to treatment of coma there is a considerable carbohydrate deficit which should be covered by energetic replacements; that carbohydrate starvation can aggravate the diabetic state; that with liver glycogen exhausted the total amount of available glucose in the body is not large despite hyperglycemia; that hypoglycemia should not be allowed to develop during insulin therapy because hypoglycemia accelerates glycogenolysis, again increasing ketogenesis; and that hyperglycemia favors hepatic glycogenesis and abolition of ketosis under certain conditions in diabetic subjects. The arguments and counterarguments on each of these points may be found in articles by Root,[38] Joslin et al.,[20] Peters,[53] Soskin,[4] Mirsky,[54] Tolstoi,[37] Franks et al.[55] and Lee et al.[56]

The physiologic evidence suggesting that early and generous administration of glucose in the treatment of coma would be beneficial appears to be sound. Nevertheless, a number of investigators have reported unfavorable results from this procedure in the treatment of severely comatose patients. Two widely separated groups of investigators[55–56] compared the behavior of patients receiving perfusions of glucose solution during the

first four to six hours of treatment with that of patients receiving only saline solutions during the same period, carrying out essentially the same treatment in all of the patients after the initial period. Both groups report that the early administration of glucose solutions led to prolonged hyperglycemia, excessive diuresis, interfered with rapid rehydration and appeared to increase mortality significantly. In the interpretation of these reports it may be surmised that it was the diuretic effect of the glucose solutions that had unfavorable consequences, not any specific ill effect of the glucose itself within the body. Hypertonic solutions of glucose tend to aggravate diuresis more than isotonic solutions. In a series of cases of coma studied on the medical wards of the Cincinnati General Hospital the intravenous perfusion of 10 per cent glucose solution has been found to provoke severe diuresis, with urinary output sometimes nearly equal to the volume of fluids administered.[57]

In the critical period just after the start of treatment, while acidosis persists and intracellular elements "continue to pour out of the cells"[46] into the plasma, any procedure leading to increased diuresis may be expected to increase the loss of electrolytes in the urine. The extra loss of electrolytes induced by increased diuresis, even for a short period, may indeed be just sufficient to influence mortality. Excessive diuresis at this time is likely to have more deleterious effects than later, after acidosis has been corrected and insulin promotes anabolic readjustments in the cells. If this speculation is valid, the reports that have been cited constitute an additional reason for the early administration of $NaHCO_3$ to correct acidosis quickly, as a step to precede the start of glucose therapy. Evidence of ill effects of the perfusion of glucose solutions during the first hours of treatment should not be allowed to detract from the validity of arguments favoring the generous administration of glucose later.

Multielectrolyte Therapy: Potassium, phosphates, etc. Numerous formulas have been devised for fluids that provide in different ways for the correction of acidosis and for the supply of intracellular as well as the extracellular electrolytes.[58–61] A basic approach to this problem has been to employ mixtures of sodium chloride and sodium bicarbonate, or of sodium chloride and sodium lactate, to provide an excess of Na over Cl such as exists normally in extracellular fluids of the body, with other elements added according to different indications or opinions as to needs. Hartman employed a modified lactate-Ringer's solution to supply small amounts of K, Ca and Mg in addition to Na; in 1929 he added more potassium but this formula was temporarily abandoned "because sometimes the richer potassium solution seemed toxic."[51] Interest in potassium therapy has, of course, been greatly stimulated by Darrow's studies on potassium metabolism in diarrheal disease of infants[62,63] and by many recent reports on the post-acidotic hypopotassemia syndrome, which emphasize the significance of potassium deficits that had long been known to exist in diabetic acidosis.

With attention focused on phosphorus metabolism, Guest and Rapoport demonstrated that the administration of Na and K phosphates intravenously and by mouth hastened the restoration of normal concentrations of phosphoric esters in the blood cells of patients and experimental subjects during their recovery from ammonium chloride acidosis, from the acidosis of diarrheal disease in infants and from diabetic acidosis.[27,30,31] We employed the Sørensen M/7.5 buffer solution, of pH 7.4, containing Na_2HPO_4 15.2 Gm. and KH_2PO_4 3.6 Gm. per L., with concentrations of Na and K, respectively, 214 and 26 m.Eq. per L. In the treatment of diabetic coma in adult patients this solution was perfused intravenously in amounts up to a liter, in combination with insulin, physiologic salt solution, sodium bicarbonate for partial correction of acidosis and glucose. Concentrations of organic acid-soluble P in the blood cells of these patients rose quickly to normal in less than twenty-four hours in contrast to the slow rise lasting four to seven days observed in other patients

similarly treated but without the phosphate solution. Concentrations of inorganic P and K in the plasma fell sharply in the early hours of treatment. The concentration of K in the cells rose closely in parallel with the increasing concentration of organic phosphates.

In 1948 Franks and co-workers described effects of the administration of a buffered solution of sodium phosphates in sixteen cases of severe diabetic acidosis, comparing the results with those observed in control subjects with fluid therapy limited to salt and glucose solutions.[64] They reported that "the administration of sodium phosphate was accompanied with a tendency toward improved utilization of carbohydrate, a rise in plasma chloride and in carbon-dioxide combining power, an apparent retention of fluid in the vascular system, a rapid clearing of the mental state and a statistically significant decrease in fatality rate." They concluded that the therapeutic regimen in diabetic coma should include parenteral administration of sodium phosphate four to eight hours after the first dose of insulin.

Butler and co-workers recently estimated the total electrolyte deficit of a volunteer subject going into severe acidosis following the withdrawal of insulin and during recovery.[29] On the basis of the metabolic balance data thus obtained they devised a formula for use in fluid and electrolyte replacement therapy that includes sodium lactate, potassium chloride, potassium phosphate and sodium chloride: 30 m.Eq. of Na, 20 m.Eq. of K, 22 m.Eq. of Cl, 5 m.Eq. of phosphate and 20 m.Eq. of lactate per L. in a solution of 5 per cent glucose. This approach seems logical but, as these investigators themselves state, before such therapy can be applied quantitatively more information is needed.

In addition to metabolic data on total losses of electrolytes in acidosis and on the eventual uptake of electrolytes by the body during recovery, there is need for more knowledge of the conditions that determine the changing ability of the tissue cells to assimilate various materials that are offered. The transfer of potassium and phosphate ions to cells is not so much dependent on their concentration in the plasma as upon enzymatic processes, which in turn are subject to the influence of changing conditions in the body fluids.

There is abundant evidence that the depleted body recovering from diabetic acidosis, given the right conditions, is capable of taking up large quantities of intravenously injected potassium salts without an abnormal rise in concentration of potassium in the plasma. Howard and Carey[65] mention an instance in which 35 Gm. of KCl (467 m.Eq. of K) were injected into a patient in eighteen hours and less than 100 m.Eq. appeared in the urine. On the other hand, deaths have occurred from the incautious administration of much smaller amounts. All investigators studying this problem caution against the dangers of hyperpotassemia arising if solutions of potassium salts are administered too rapidly or too early in the treatment of coma, when the plasma potassium level is elevated, especially in the presence of renal impairment.

In the treatment of severely comatose patients when even without complete chemical studies the need for potassium is reasonably certain, it seems desirable and safe to administer 1 Gm. of KCl each hour for four doses, as now practiced in a number of centers. The first dose may be started at around the fourth hour of treatment, after acidosis has been partially corrected by the administration of sodium bicarbonate and when insulin is becoming increasingly effective. Since relatively small amounts of KCl have afforded prompt relief of severe symptoms of respiratory paralysis, as in Holler's original case, conservative dosage of this sort should suffice in most cases to prevent any acute manifestation of potassium deficiency. The time at which minimal corrective therapy is offered, if properly directed to negotiate each critical phase in coma and recovery, may be more important than speed in the replenishment of total deficits. After a patient has successfully passed through the critical early period of

recovery further restoration of the body stores and a more normal nutritional state can be accomplished efficiently by oral feeding.

Whole Blood and/or Plasma. The problems of the restoration of circulating blood volume in the treatment of severe coma with circulatory collapse are similar to those encountered in the treatment of surgical shock. When acidosis has been of short duration and dehydration abrupt, in patients whose previous nutritional state was good, hematocrit values and concentrations of plasma protein are apt to be high, indicating hemoconcentration. In such cases the administration of salt solution serves adequately to restore the circulating plasma volume. But if the concentration of plasma protein is normal or low at the start of treatment, it may fall sharply with dilution and the perfused salt solution may tend to leave the circulation. In such circumstances, and in any case if the blood pressure does not respond to the administration of saline fluids, whole blood or plasma transfusions should be administered promptly. This need is encountered more frequently in older patients than in young adults, rarely in children, in our experience.

Vitamins. Several factors of the vitamin B-complex (thiamine, riboflavin, niacin) are essential to the enzyme systems involved in carbohydrate metabolism. Although there is no reason to believe that vitamin deficiencies are concerned in the etiology of diabetes, mutually aggravating factors can be defined in the metabolic disturbances of co-existent diabetes and avitaminosis.[66] Vitamin deficiencies in diabetic subjects lead to increased needs for insulin; on the other hand, the stimulation of carbohydrate metabolism by the administration of insulin and glucose in the treatment of coma abruptly increases the body's needs for the vitamins. A diabetic crisis, coma and recovery may precipitate frank manifestations of avitaminosis in subjects with previously unrecognized deficiency states, with symptoms usually blossoming during periods of increased food intake and rapid gain of weight. Hence, it is a well justified common practice in many clinics to administer multivitamin B preparations with intravenous fluids during the treatment of coma and to continue generous amounts by mouth, supplementing realimentation in the recovery period. Inasmuch as phosphorylation of the vitamins into active forms in the body may be slow in diabetic acidosis,[67] it has been suggested that the use of phosphorylated preparations (when available) might be more quickly effective. Boulin, Uhry and co-workers[24a] and Markus and Meyer[24b] have reported the use of a crystalline preparation of thiamine-pyrophosphate (cocarboxylase) in the treatment of coma. These authors offer the thesis that an important disturbance of carbohydrate metabolism in diabetic coma is involved at a stage in the Krebs tricarboxylic acid cycle in which insulin is not involved but cocarboxylase is essential for the conversion of pyruvate; that the difficulty at this stage accounts for the finding of high blood-pyruvate levels in diabetic coma and that slowing of the disposal of pyruvate interferes with other phases of carbohydrate metabolism in which insulin is involved. They claim for the scheme of treatment in which cocarboxylase was employed (100 mg. cocarboxylase plus 10 mg. riboflavin) some reduction in the duration of coma and a considerable reduction in total requirements for insulin (in a small series of ten patients) compared with results previously obtained in the same clinic.

The Prevention of Diabetic Acidosis and Coma. Under any system of diabetic control, whether with rigid regimentation of a "prescribed-diet-aglycosuric regimen," or with liberal rules of the so-called "free-diet-glycosuric regimen," instructions for home management should emphasize unceasingly the signs of impending trouble to which the patients (or parents of young diabetics) should be alert: excessive diuresis, loss of weight and acetonuria. Rapidly increasing ketonuria is the most dependable sign heralding the incipient development of a diabetic crisis, more dependable than glycosuria as an index of the physiologic state of

the liver with regard to its glycogen store and cellular metabolism. Frequent testing of the urine for acetone should be an essential part of any scheme for self-management. Use of the convenient acetone-test powders[68] that are now commercially available makes this test easy, the least onerous task of the patient's daily routine at home or elsewhere.

It is especially urgent that tests of the urine for acetone be done during any illness, whether mild or severe, with respiratory and gastrointestinal infections, diarrhea, vomiting, fever, the contagious diseases of childhood, etc.; also, at times of physical injuries, unusual excitement, emotional stress. When acetonuria is discovered under any of these circumstances, extra insulin should be taken promptly. The development of a crisis can be more easily arrested by extra doses of insulin when acetonuria first appears than later when the progressive development of acidosis involves factors that diminish the effectiveness of insulin.

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Clinical Studies

Changes in the Volume of the Plasma, Interstitial and Intracellular Fluid Spaces During Hydration and Dehydration in Normal and Edematous Subjects*

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RECENT investigations indicate that both the plasma volume[1–5] and the intracellular fluid space[6,7] are responsive to changes in hydration. These observations are in opposition to the concept that the "losses of extracellular fluid from the vascular compartment caused by abnormal circumstances are observed to be immediately replaced at the expense of interstitial fluid."[8]

The present investigation was undertaken to determine the extent of the contribution of each fluid compartment to the gain or loss of total body water during states of excessive hydration or dehydration in normal subjects and after diuresis in edematous patients. In addition changes in the hematocrit and plasma protein concentration were assessed as to their reliability in predicting changes in plasma volume during fluctuations in hydration.

MATERIAL AND METHODS

The normal subjects were young adult males admitted to the wards of the Evans Memorial Hospital for treatment of uncomplicated latent or primary syphilis. All subjects were afebrile and exhibited no cardiovascular or renal abnormalities. The edematous patients comprised a heterogeneous group with various diagnoses. (Table I.)

Immediately following control determinations in both normal and edematous subjects, dehydration was carried out by instituting a regimen of fluid restriction to 1,000 cc. daily, a diet containing a total of 0.8 Gm. of sodium per day and administration of 6 Gm. of ammonium chloride daily. On the evening of the fourth day 2 cc. of mercuhydrin were injected intravenously and the experimental observations were repeated on the morning of the fifth day.

Excessive hydration was produced in normal subjects by administering daily doses of 25 Gm. of sodium chloride orally and 10 mg. of desoxycorticosterone acetate intramuscularly for a period of five days with fluids and diet *ad libitum*. Control determinations were accomplished immediately prior to the institution of this regimen, and experimental observations were carried out on the morning of the fifth day. In three of these subjects 2 cc. of mercupurin were injected intravenously on the evening of the fifth day followed by a further series of experimental observations on the morning of the sixth day.

The methods used for determining plasma volume, plasma protein, hematocrit value and "thiocyanate space" have been previously reported[9] except that in the edematous patients a period of six rather than two hours was allowed for equilibration of thiocyanate. The thiocyanate space represents the total volume in which thiocyanate is distributed, including the plasma, red cells and interstitial fluid. Although thiocyanate measures a larger space than that actually occupied by the extracellular

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fluid volume, other methods available to clinical medicine, such as the chloride and sodium spaces, suffer from similar disadvantages.[10] Furthermore, since the cellular elements which all of these electrolytes enter change in volume very slowly, the changes observed in the volume distribution of such substances during acute experiments probably represent gains or losses of extracellular fluid. Because of the simplicity of the thiocyanate method, it has greater advantage in clinical studies than other methods. Until such time as practical and accurate measurements of extracellular fluid volume are devised, the methods

TABLE 1

THE CHANGES IN PLASMA VOLUME AND TOTAL EXTRACELLULAR (AVAILABLE) FLUID FOLLOWING HYDRATING AND DEHYDRATING PROCEDURES IN NORMAL INDIVIDUALS AND IN PATIENTS WITH DISTURBED WATER BALANCE

Subject	Age	Diagnosis	Procedure	Plasma Volume (cc.)			Available Fluid (cc.)			Plasma Volume Change‖ / Available Fluid Change
				Before	After	Gain or Loss	Before	After	Gain or Loss	
J. D.	20	Primary syphilis	Dehydration*	2970	2760	−210	20,250	19,250	−1000	.21
E. L.	28	Primary syphilis	Dehydration*	3590	2490	−1100	20,200	17,800	−2400	.46
J. G.	23	Latent syphilis	Dehydration*	2820	2240	−580	19,800	19,200	−600	.97
V. B.	23	Primary syphilis	Dehydration*	3300	2960	−335	17,250	15,900	−1350	.25
						−555			*−1340*	*.47*
D. J.	72	Hypertension, cardiac failure	Dehydration†	3450	2775	−675	34,600	16,650	−17,950	.04
D. E.	40	Cirrhosis, ascites	Dehydration†	4940	4700	−240	34,200	28,500	−5700	.04
B. G.	58	Hypertension, Paget's disease, cardiac failure	Dehydration†	3090	2695	−315	33,400	14,700	−18,700	.01
C. F.	74	Chronic nephritis, cardiac failure	Dehydration†	4270	3580	−690	29,400	22,900	−6500	.11
						−480			*−12,210*	*.05*
W. S.	24	Primary syphilis	Hydration‡	2820	3420	+600	21,500	24,800	+3300	.18
R. L.	37	Latent syphilis	Hydration‡	3010	3600	+590	21,650	28,100	+6450	.09
E. N.	31	Primary syphilis	Hydration‡	3330	3690	+360	17,400	20,800	+3400	.11
A. L.	30	Primary syphilis	Hydration‡	3120	3690	+570	19,400	24,800	+5400	.11
						+525			*+4640*	*.12*
R. L.	37	Latent syphilis	Dehydration§	3600	3000	−600	28,100	22,500	−5600	.11
E. N.	31	Primary syphilis	Dehydration§	3690	3260	−430	20,800	16,450	−4400	.10
A. L.	30	Primary syphilis	Dehydration§	3690	2945	−745	24,800	17,250	−7550	.10
						−410			*−5850*	*.10*

* Normal subjects dehydrated with low sodium diet, NH_4Cl and mercuhydrin.

† Edematous patients dehydrated with low sodium diet, NH_4Cl and mercuhydrin

‡ Normal subjects hydrated with excess sodium chloride and desoxycorticosterone acetate.

§ Normal subjects previously hydrated as in ‡ acutely dehydrated with single dose of mercuhydrin.

‖ This value expresses the per cent gain or loss of total extracellular (available) fluid contributed to by the change in the plasma volume.

(Mean values in italics.)

used in this study must suffice with the realization that they are at best crude indicators of quantitative changes.

The difference between the changes in the thiocyanate space and the plasma volume after hydration or dehydration represented the changes in the interstitial fluid space. Because of the absence of methods of determining the intracellular fluid space directly in man, the difference between the change in body weight in Kg. and the thiocyanate space in L. was used to calculate the change in intracellular fluid volume. It was assumed that since these patients were not acutely ill their food intake and tissue breakdown were relatively constant during the experiment and therefore the changes in weight represented almost entirely changes in total body water. Further, the experimental periods were never greater than five days. Again, the changes observed in intracellular fluid space should be considered as representing approximate rather than precise numerical values.

All determinations were carried out in the morning with the patient in the postabsorptive state, resting supine in a warm room for at least one-half hour prior to drawing the first blood samples; venipunctures were accomplished with minimal stasis. After these determinations were completed the arterial pressure was recorded with an arm cuff and the subjects were weighed on a beam balance accurate to ± 2 Gm.

RESULTS

Relative Changes in Plasma Volume and Interstitial Fluid Space. When four normal subjects were dehydrated by the method just described, the mean decrease in plasma volume was 555 cc. (range 210 to 1,100 cc.) while the mean reduction in total extracellular (thiocyanate) space was 1,340 cc. (range 600 to 2,400 cc.). Thus the plasma volume contributed an average of 47 per cent of the decrease in total extracellular fluid (range 21 to 97 per cent).

In the four edematous patients subjected to the same regimen of dehydration the plasma volume contributed only 4 to 11 per cent (mean 5 per cent) of the decrease in the thiocyanate space. The absolute decrease of 240 to 690 cc. (mean 480 cc.) in plasma volume was approximately the same as in the normal subjects but the reduction in the thiocyanate space was almost ten times as great (Table I) ranging from 5,700 to 18,700 cc. with a mean of 12,210 cc.

When four normal subjects were overly hydrated with an excess of salt and desoxycorticosterone acetate, the thiocyanate space increased by 3,300 to 6,450 cc. (mean 4,640 cc.). Again the mean increase in plasma volume of 527 cc. (range 360 to 600 cc.) gained during excessive hydration was quite similar in amount to the mean decrease in plasma volume during dehydration. However, due to the apparently marked gain in interstitial fluid the increase in plasma volume made up only 9 to 19 per cent (mean 12 per cent) of the change in the total extracellular (thiocyanate) space.

When three normal subjects thus excessively hydrated were subjected to a sudden diuresis by an intravenous administration of mercupurin, the plasma volume and thiocyanate space decreased in almost exact proportion as they had increased. As a result the plasma volume contributed 10 to 11 per cent of the decrease in the "total extracellular space," in contrast to the much greater percentage contribution made by the plasma volume when normally hydrated individuals were dehydrated. (Table I.)

Relative Changes in Total Extracellular and Intracellular Fluid Spaces. The four normal subjects who were dehydrated by the regimen just described lost 0.6 to 2.4 L. of fluid (mean 1.3 L.), from the total extracellular (thiocyanate) space. (Table II.) During this period the loss of body weight ranged from 2.1 to 2.9 Kg. with a mean of 2.6 Kg. Since 1 L. of fluid weighs 1 Kg., the difference between the amount of weight loss in Kg. and the total extracellular fluid loss in L. was taken to represent approximately the change in intracellular fluid space. Calculated thus the intracellular fluid space decreased by 0.5 to 2.2 L. (mean 1.2 L.). The proportion of total body water loss contributed by the total extracellular fluids varied from 22 to 83 per cent (mean 52 per cent), the remainder

presumably being made up from the intracellular fluid space.

In edematous patients similar dehydrating procedures produced far greater drains in extracellular fluid. The thiocyanate space decreased by 5.7 to 18.7 L. (mean 12.2 L.) while body weight decreased by 7.7 to 22.7 Kg. (mean 13.6 Kg.). The total extracellular (thiocyanate) space contributed 72 to 126 per cent (mean 88 per cent) of the change in total body water. (Table II.) In patient B. G., Table II, almost 4 L. of fluid appeared to move into cells since the thiocyanate space decreased 18.7 L. while the body weight decreased by the lesser amount of 14.9 Kg. In the remaining patients the intracellular losses of 2.0 to 4.75 L. were slightly greater than the decreases in the non-edematous normal individuals. However, due to the greater changes in the thiocyanate space in the edematous patients, the proportionate loss of intracellular fluid averaged only 22 per cent of the total body water as contrasted to 48 per cent in the normal subjects.

The excessive hydration produced in normal subjects by administration of salt and desoxycorticosterone acetate appeared

TABLE II

CHANGES IN TOTAL EXTRACELLULAR (AVAILABLE) FLUID AND BODY WEIGHT FOLLOWING HYDRATING AND DEHYDRATING PROCEDURES IN NORMAL INDIVIDUALS AND IN PATIENTS WITH DISTURBED WATER BALANCE

Subject	Body Weight (Kg.)			Available Fluid Gain or Loss Liters‖	Calculated Intracellular Fluid Gain or Loss (L.)	Available Fluid Change ¶ / Body Weight Change
	Before	After	Gain or Loss			
J. D.*	72.7	70.2	−2.5	−1.0	−1.5	0.40
E. L.*	65.7	62.8	−2.9	−2.4	−0.5	0.83
J. G.*	74.4	71.6	−2.8	−0.6	−2.2	0.22
V. B.*	62.5	60.4	−2.1	−1.35	−0.75	0.64
Mean			−2.6	−1.3	−1.3	0.52
D. J.†	63.2	40.5	−22.7	−17.95	−4.75	0.79
D. E.†	84.6	76.9	−7.7	−5.7	−2.0	0.74
B. G.†	51.4	36.5	−14.9	−18.7	+3.8	1.26
C. O.†	75.2	66.1	−9.1	−6.5	−2.6	0.72
Mean			−13.6	−12.2	−1.4	0.88
W. S.‡	72.4	75.5	+3.1	+3.3	−0.2	1.06
R. L.‡	80.2	84.0	+3.8	+6.45	−2.65	1.70
E. N.‡	61.2	63.9	+2.7	+3.4	−0.7	1.26
A. L.‡	72.6	75.8	+3.2	+5.4	−2.2	1.68
Mean			+3.2	+4.6	−1.9	1.67
R. L.§	84.0	79.2	−4.8	−5.6	+0.8	1.17
E. N.§	63.9	60.6	−3.3	−4.4	+1.1	1.33
A. L.§	75.8	72.1	−3.7	−7.55	+3.85	2.04
Mean			−3.9	−5.85	+1.9	1.13

*, †, ‡, §, same notations as in Table I.

‖ Values derived from Table I.

¶ Expresses the per cent of weight gain or loss contributed by the change in total extracellular (available) fluid.

to result in a movement of fluid out of the intracellular into the extracellular space. Thus, whereas the mean increase in the thiocyanate space was 4.6 L. (range 3.3 to 5.45 L.) the mean increase in body weight was only 3.2 Kg. (range 2.7 to 3.8 Kg.). The apparent decrease in intracellular fluid, therefore, averaged 1.9 L. with a range of 0.2 to 2.65 L.

However, when mercuhydrin was administered intravenously to these overly hydrated subjects, the fluid shifts were such as to restore within twelve hours the approximate pretreatment control conditions. In the three subjects studied the mean decrease in thiocyanate space was 5.85 L. (range 4.4 to 7.55 L.) and body weight was 3.9 Kg. (range 3.3 to 4.8 Kg.), an apparent mean gain in intracellular fluid volume of 1.9 L. (range 0.8 to 3.85 L.). Thus mercupurin appeared to be a specific antagonist of the salt and desoxycorticosterone acetate effect.

Relation of Changes in Hematocrit Value and Plasma Protein Concentration to Changes in Plasma Volume. To calculate the change in plasma volume from the hematocrit values the following formula was used:

$$\Delta PV = \frac{H_1 - H_2}{H_2(1 - H_1)}$$

ΔPV represents the change in plasma volume, H_1 the original hematocrit and H_2 the hematocrit value following dehydration or hydration. The ratio of the per cent change in plasma volume as determined by the dye method to the per cent change as calculated from the hematocrit values varied from unity by 0.4 to 2.12 (mean 0.93, S.D.0. 24). The correlation coefficient calculated from the equation

$$r = \frac{\Sigma x_1 x_2}{\sqrt{(\Sigma x_1^2)(\Sigma x_2^2)}}$$

was 0.49. Thus, although the change in hematocrit value indicated the directional change in plasma volume in every instance, it failed to determine quantitative change accurately.

The ratio of the per cent change in plasma volume to the per cent change in plasma protein varied from unity by 0.5 to 1.6 (mean 1.3, S.D. 0.18). The correlation coefficient was 0.68. The change in plasma protein concentration, therefore, seemed to indicate the degree of plasma volume change more accurately than the hematocrit. However, the agreement was not sufficiently close to warrant quantitative estimation.

Changes in Arterial Pressure. In the dehydrated subjects no significant changes in arterial pressure were noted in the supine position although one patient complained of faintness in the erect position following diuresis.[11] In all of the normal subjects who were given salt and DCA in excess, the supine mean arterial (one-half the sum of the systolic and diastolic) pressure rose slightly, the mean rise being 10.6 per cent (range 6.7 to 15.2 per cent).

COMMENTS

The results of this investigation suggest that neither the plasma volume nor the intracellular fluid volume are static under conditions of changing hydration. During dehydration in normal subjects approximately 25 per cent of the loss of total body water was contributed by the plasma volume, 25 per cent by the interstitial fluid and 50 per cent by the intracellular fluid. Mellers, Muntwyler, Meutz and Abbot[2] also observed a marked reduction of plasma volume in dogs who were dehydrated by various procedures including the intraperitoneal injection of 5 per cent glucose, starvation and the production of pancreatic fistulas.

In contrast, similar dehydrating procedures in patients with gross edema produced a loss of total body water of which approximately 5 per cent was supplied by the plasma volume, 85 per cent by the interstitial fluid and 10 per cent by the intracellular fluid. However, despite the smaller percentage changes of plasma and intracellular fluid volumes the absolute amount of fluid loss from these compart-

ments usually was approximately the same in both the normal and the edematous subjects, the difference in proportion being due to the far greater absolute losses of interstitial fluid in the edematous patients. It is evident that with the greater diuresis in edematous as contrasted to normal individuals the plasma volume must contribute a smaller percentile loss to the fluid depletion of edematous subjects in order to prevent excessive hemoconcentration.

When normal subjects were overly hydrated with excess salt and desoxycorticosterone acetate, the interstitial fluid took up relatively large amounts of water. As a result the plasma volume gain averaged only 12 per cent of the increase in total extracellular (thiocyanate) space although the absolute increase in plasma volume was similar in amount to the reduction occurring during dehydration of normal subjects. The intracellular fluid volume appeared to *decrease* during this period, with an average shift of almost 2 L. of fluid from the intracellular to the extracellular space. A similar fluid shift following desoxycorticosterone acetate has been noted previously by Loeb and his associates[12] in a patient with Addison's disease. Also a slight decrease in the intracellular water of muscle tissue after desoxycorticosterone acetate administration has been observed in dogs by Harkness and his associates.[6] In addition, they noted considerable replacement of intracellular potassium with sodium. It should be noted that the apparent decrease in intracellular fluid space presumes that the distribution of thiocyanate is the same after as compared to before DCA. However, it is possible that the thiocyanate ion may penetrate cells to a greater extent after DCA, due to possible changes in cellular permeability produced by the drug, with the result that the shift of fluid from the cells to the interstitial compartment would be more apparent than real.

Following the injection of mercuhydrin, there appeared to be a specific reversal of this DCA effect, with a return of plasma volume, thiocyanate space and body weight to approximate pretreatment values. These changes toward normal indicated an apparent shift back into the intracellular space of the fluid previously lost to the extracellular compartment.

Although the plasma volume and intracellular fluid space appeared to fluctuate in both normal and edematous patients with changes in hydration, the absolute amount of change in these fluid compartments appeared to be relatively constant under the varied conditions of these experiments. The mean decrease in plasma volume with dehydration in normal subjects agrees closely with the plasma volume reductions observed by Lyons, Avery and Jacobson[1] in a similar experiment while the mean increase in plasma volume in overly hydrated patients is in good agreement with the increases of plasma volume observed by Clinton and Thorn[4] who also produced excessive hydration in normal individuals with DCA. While such uniformity may be fortuitous, it suggests that relatively constant fractions of the plasma volume and possibly the intracellular fluid space are able to shift during changes in hydration. It is possible that greater changes in plasma and intracellular fluid volume would occur only under more drastic conditions than those induced during these studies.[2]

However, the interstitial fluid space appeared to take up relatively large amounts of fluid, and once having taken up an excess appeared to contribute a larger share to the diuresis resulting from dehydrating procedures. Thus beyond certain limits the interstitial fluid space appeared to "spare" the plasma and intracellular fluid volumes. This relatively great capacity of the interstitial fluid space was not apparent, however, in the dehydrated normal patients. Although the degree of dehydration was not excessive in these experiments, the fact that clinically the hematocrit may rise to high values during dehydration suggests that the ability of the interstitial fluid space to spare plasma volume is not as great during severe dehydration as it is during excessive hydration.

The changes in the hematocrit value and plasma protein concentration reflected qualitatively rather than quantitatively the fluctuations in plasma volume and would seem to have value clinically only as rough guides to the directional changes in plasma volume. Since in the absence of hemorrhage the red cell volume is relatively stable, it appeared somewhat surprising that the hematocrit change should be less accurate a measure of plasma volume shifts than the change in plasma protein concentration. However, since the hematocrit value differs in the small as contrasted to the large vessels,[13] the venous blood samples do not measure accurately the total body hematocrit. Further, it is possible that some redistribution of the fluid and cellular elements of the blood may occur under conditions of changing body hydration.

SUMMARY AND CONCLUSIONS

Determinations of plasma volume (T-1824), thiocyanate space, body weight, hematocrit value and plasma protein concentration carried out before and after hydrating and dehydrating procedures in man revealed that:

1. During acute dehydration produced by salt and fluid restriction plus ammonium chloride and mercupurin in four normal subjects the plasma volume and interstitial fluid space each contributed approximately 25 per cent of the total weight loss. By inference the intracellular fluid apparently contributed 50 per cent of the loss.

2. During similarly induced dehydration in four edematous patients the interstitial fluid compartment contributed approximately 85 per cent, the plasma volume approximately 5 per cent and the intracellular fluid space 10 per cent of the body water loss.

3. The greater percentage loss of total extracellular fluid in the edematous as contrasted with the normal subjects was due to the greater absolute amount lost from the interstitial fluid space in the edematous patients. The absolute loss of plasma and intracellular fluid volumes was essentially similar in the edematous and normal individuals.

4. During excessive hydration of four normal subjects with salt and desoxycorticosterone acetate there was a proportionately great increase in interstitial fluid volume, a proportionately less increase in plasma volume and an apparent shift of fluid from the intracellular to the extracellular compartment. Mercuhydrin appeared to reverse this abnormal distribution of body water after DCA.

5. The absolute amounts of gain or loss from the plasma volume and the calculated intracellular fluid space were relatively constant under the conditions of these experiments, the proportionate differences being accounted for by the lability of the interstitial fluid space.

6. The per cent changes in hematocrit value and plasma protein concentration during these studies indicated qualitatively but not quantitatively the per cent changes in plasma volume.

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Insulin Mixtures*

Experiences in the Use of Extemporaneous Bottle Mixtures in Diabetic Clinic Patients

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THE principle of prolonged action has been the basis of a number of refinements in the management of diabetes mellitus since the introduction of protamine zinc insulin in 1935. The latent period after injection soon proved to be the major defect in the mechanics of this insulin although it is of no importance in the milder cases requiring up to 40 units of insulin daily to produce a normal fasting blood sugar. In the severer diabetics there is either a postprandial hyperglycemia, particularly after breakfast, or frequent early morning hypoglycemia when the insulin dosage is increased to avoid this. These diabetics must then be given additional unmodified insulin for its immediate effect, as well as protamine zinc insulin which controls the morning blood sugar. Satisfactory control for a number of diabetics could be achieved only by two or more injections of insulin daily with greater care being required to avoid untoward side effects.

Attempts to develop a preparation with the depot action of protamine zinc insulin combined with the immediate effect of unmodified insulin were the logical result. Several reports on the injections of the two insulins in combination appeared, but it was not until 1941 that Ulrich[1] pointed out that thorough mixing was necessary to achieve predictable results. He found that the excess protamine was utilized to produce more long-acting insulin and that less than one part of regular insulin to one part protamine produced no change in action of the mixture. Equal parts or more of unmodified insulin resulted in a preparation with characteristics of both types, and he showed that a 3:2 mixture controlled postprandial glycosuria. This most promising innovation was investigated in more detail by a number of other workers, and the time-activity and approximate proportionate insulin contents of different mixtures were worked out.[2–6] Other modifications have been investigated,[7,8] but extemporaneous mixtures modified to fit the needs of the individual patient seem to have the most established usefulness.[9–17]

The routine of management of diabetes mellitus in the Diabetic Clinic of the Medical College of Alabama must be gauged to the low educational and economic level of the clinic population. Until 1944 severe diabetics were treated with large doses of protamine zinc insulin and a postprandial spill was tolerated. Very few of the patients were capable of following a regimen of rigid diet and multiple doses of unmodified insulin with a single dose of protamine zinc insulin. Despite simplification of diet and a minimum of insulin injections, cooperation was poor and episodes of acidosis and insulin reactions were far too frequent. In 1944 a cautious trial of insulin mixtures was begun in those patients presenting the greatest problems in control. It was found almost at the outset that mixing of the insulins in a syringe as

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described in all of the published reports at that time was too complex a procedure in this type of individual. For this reason the first patients were hospitalized and given standardized mixtures prepared in the syringe in this manner. They were then changed over to a mixture of the same proportion prepared in a bottle. Mixtures prepared in amounts up to 1,600 units at one time gave no clinical results appreciably different from that expected of those prepared in the syringe, and after some experience patients were changed directly from protamine zinc insulin or a combination of insulins to a premixed preparation. During the course of this study a report appeared which confirms our finding that after the original changes occur in mixing the insulin no further alteration in action is apparent due to the time elapsing before the insulin is used.[17]

TABLE I
GUIDE FOR MIXING INSULIN

Mixture	Bottles Prescribed		Insulin Per Bottle		Excess		Final Amount of Mixture
	Regular	PZI	Regular	PZI	Regular	PZI	
1:1	1	1	5 cc.	5 cc.	0	0	20 cc.
3:2	2	1	6 cc.	4 cc.	+2 cc.	−2 cc.	30 cc.
2:1	2	1	6.5 cc.	3.5 cc.	+0.5 cc.	−0.5 cc.	30 cc.
7:3	2	1	7 cc.	3 cc.	−1 cc.	+1 cc.	30 cc.
3:1	2	1	7.5 cc.	2.5 cc.	−2.5 cc.	+2.5 cc.	30 cc.

All patients on insulin mixtures were given one of the standard clinic diets. These consist of moderately high carbohydrate allowances in the following proportions:

1,280 calories, 120 Gm. CHO
1,510 calories, 150 Gm. CHO
1,750 calories, 165 Gm. CHO
1,900 calories, 180 Gm. CHO
2,000 calories, 200 Gm. CHO

The diet outline is presented in household measures, and each patient keeps a notebook which is checked by the dietitian at every clinic visit. Additions or subtractions are made to these standard diets as excess weight or physical activity may indicate.

Fasting blood sugar and urinalysis are obtained at each visit, and a blood sugar level of 90 to 130 mg. per cent is taken to indicate satisfactory control. The insulin prescription is prepared and the clinic nurse mixes the insulin for the patient during the visit in amounts calculated to last until the next appointed visit.

TABLE II
252 CONSECUTIVE REGISTRATIONS OF DIABETIC CLINIC PATIENTS

	No. of Cases	% of Total	Sex		Race		Mean Age
			Male	Female	White	Colored	
Diet alone	33	13	3	30	7	26	51
PZI only	151	60	40	111	55	96	53.4
PZI plus regular	1	0.4	1	0	1	0	65
Mixtures	67	26.6	25	42	32	35	36.5
Totals	252	....	69	183	95	157	48.7

All precautions are taken to avoid contamination. Sterile empty insulin bottles are available to facilitate mixing without excessive transferring of the material. The nurse responsible for mixing the insulin is guided by a chart which has been prepared for this purpose. (Table I.) Care is taken that the syringes are freshly sterilized and the bottle tops are thoroughly cleansed with alcohol. The proper amount of insulin is withdrawn from a new vial containing 10 cc. The other type insulin is then added as indicated, care being taken first to withdraw the proper amount of air so that excessive foaming does not occur. Excess insulin which results is kept and used to make up a deficit in a later mixing. One or two extra vials of insulin ensure the prevention of any waste at all.

Twenty-four-hour urine specimens are not obtained but in some cases it has been possible to have the patient record urinalyses for sugar three times daily. If a patient suffers from numerous reactions or if there is persistent hyperglycemia, hospitalization is instituted.

An analysis of 252 consecutive clinic registrations is presented in Table II. The thirty-three patients controlled on diet

alone represent 13 per cent of the group with a mean age of fifty-one years. Protamine zinc insulin given as one injection in the morning before breakfast is employed in 151 cases or 60 per cent of the total, the mean age being 53.4 years. Only one patient received supplementary unmodified insulin injections in addition to depot insulin. The patients with the more severe cases that in the past have had to have such treatment are included in the group of sixty-seven patients given insulin mixtures. This represents 26.6 per cent of the patients with a mean age of 36.5 years. The marked difference in the mean age of those on mixtures as compared with those on protamine alone or diet is illustrative of the younger, more severe diabetics requiring the mixture. The clinic population as a whole is pictured in this tabulation. The greater proportion of colored to white patients illustrates the composition of the clinic population of a southern charity out-patient department.

TABLE III
ANALYSIS OF PATIENTS ON INSULIN MIXTURES

Mixture	Total No.	% of Total	Male	Female	White	Colored	Mean Age	Mean Dosage
1:1	28	41.8	10	18	17	11	34.9	59.7
3:2	1	1.5	1	0	0	1	30	65
2:1	27	40.3	10	17	15	12	37.7	69.9
7:3	7	10.4	3	4	0	7	39.8	68
3:1	4	6.0	1	3	0	4	35.2	62.5
Total	67	....	25	42	32	35	36.5	64.9

Table III presents an analysis of the sixty-seven patients receiving mixtures, all using premixed bottle mixtures. The greatest group, twenty-eight cases or 41.8 per cent, are on a 1:1 mixture with a mean dosage of 59.7 units. The next largest group is that given two parts of unmodified insulin to one part of protamine zinc. There were twenty-seven patients on this 2:1 mixture representing 40.3 per cent with a mean dosage of 69.9 units. This difference in total dosage is probably significant and is in keeping with the experience of others who find that the greater the total dosage, the greater the requirement of unmodified insulin in proportion to protamine. Other ratios are used much less frequently, but any proportion may be mixed to suit the demands of the individual patient.

There has been no attempt to obtain a control group by keeping a part of the group on protamine and supplementary unmodified insulin, mainly because of the previous difficulties encountered in this method of treatment. It is possible to compare the behavior of patients with records of several years of treatment prior to being placed on bottle mixtures. Three cases representative of satisfactory results are briefly presented:

CASE REPORTS

CASE I. H. T., aged twenty-two, was a negro male. This patient was admitted October 15, 1942, at which time diabetes was diagnosed. He was discharged after being given 60 units of protamine zinc insulin. On October 16, 1943, he was re-admitted in diabetic acidosis. Fifty units of protamine zinc insulin was the dose on discharge. Control remained generally unsatisfactory and on July 10, 1947, he was re-admitted for standardization and discharged on 65 units of a 2:1 mixture. He has required no admission since this date and control has been more satisfactory.

CASE II. S. I., aged forty-four, was a negro male. Diabetes was diagnosed elsewhere in 1924 or 1925, and he was first seen in the clinic on July 24, 1945. He was placed on 80 units of protamine zinc insulin daily and remained on this dosage until March 29, 1946, during which time his blood sugar ranged from 96 to 310 mg. per cent. He was then placed on 65 units of a 7:3 mixture which was gradually decreased to 45 units. His blood sugars have ranged from 60 to 180 mg. per cent with one exception; there have been no severe reactions or hospital admissions.

CASE III. E. M. B., aged eighteen, was a negro female. Diabetes was diagnosed in 1935, and treatment with insulin was begun elsewhere in 1936. She was first seen in the clinic on March 20, 1945, and given 40 units of protamine zinc insulin twice daily. On September 6, 1945, she was admitted in mild acidosis. She was placed on a 2:1 mixture on September 20th and was discharged using 90 units of a 2:1

mixture. On October 18, 1945, she was changed to a 7:3 mixture. She was re-admitted to the hospital on December 29, 1945, in acidosis accompanying acute tonsillitis. Upon discharge she was given a 1:1 mixture, 90 units in divided doses, morning and evening. In June, 1947, elective tonsillectomy was performed, and she was discharged taking 100 units of a 2:1 mixture given in one daily morning dose. She did so well that she lapsed in her clinic visits after December, 1947, and was not seen again until April 14, 1948, when she was admitted to the hospital with polyarthritis, hypertension and mild acidosis. Since her discharge, she has been well regulated on a dosage of 95 units of a 2:1 mixture.

Some of the patients show poor control on mixtures but often there is complete disregard of diet and irresponsibility in reporting complications. The fourth case is presented as an example of this type:

CASE IV. L. C., aged sixteen, was a white female. Diabetes was diagnosed at the age of four. She was first treated in the clinic in July, 1945, and given protamine zinc insulin. Hospital admissions were necessary in September, 1945 for diabetic leg ulcers and in August, 1946, for impetigo. After the second admission she was discharged on 90 units of a 2:1 mixture. On November 9, 1946, the dosage was changed to 65 units of a 3:1 mixture with no improvement in control. On April 7, 1947, she was admitted in acidosis and precoma accompanied by acute pharyngitis. Upon recovery she was discharged on 90 units of a 3:2 mixture. A fourth admission occasioned by acidosis occurred in June, 1947, and she was discharged on 80 units of a 2:1 mixture. On July 2, 1947, she was admitted with an abscess of the right thigh, apparently due to use of an unsterile insulin syringe. Culture of the insulin revealed no organisms to be present. On September 15th she was again admitted with an abscess of the thigh, and after incision and drainage she was discharged using 75 units of a 2:1 mixture. There have been no subsequent admissions, but control has been poor on 75 to 80 units of a 2:1 mixture, the blood sugar ranging from 58 to 263 mg. per cent.

In addition to poor control due to improper cooperation, Case IV represents one of two instances of abscess formation that have occurred in patients receiving premixed insulin. The possibility of contamination in mixing the insulins was seriously considered at the outset, but it was believed that there was less chance of infection in mixing the insulins under ideal conditions in the clinic than there would be in allowing these patients to take multiple injections at home or to attempt to mix the insulins in the syringe. Despite the mixing of from two to four vials of insulin at one time, the unsterile syringe remains the greatest hazard insofar as infections are concerned.

SUMMARY AND CONCLUSIONS

An analysis of 252 diabetic clinic patients is presented, sixty-seven of whom have been under treatment with insulin mixtures.

Insulin mixtures have a place in the management of severe diabetics, juvenile diabetics and moderately severe adult diabetics. The necessity of multiple injections is avoided, and control is more satisfactory than with one injection of protamine zinc insulin and supplementary injections of unmodified insulin.

Insulin mixtures may be premixed in the desired proportion in the bottle with no change in action apparent clinically and with little danger of infection.

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Review

Cardiac Complications of Diabetes Mellitus*

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DIABETES mellitus is a metabolic disease. Even if the abnormal metabolism remains well controlled, however, the complications of the chronic disease are frequent, widespread and often permanent. Among the most common of these complications is heart disease. The heart is also involved occasionally when control of the disease is temporarily out of hand. Such lack of control may be in the nature of acute undertreatment (acidosis) or accidental overtreatment (hypoglycemia), and each of these states may give rise to cardiac complications. This paper is a summary of these cardiac complications of diabetes mellitus.

COMPLICATIONS OF THE CHRONIC DISEASE

Coronary Artery Sclerosis. It has been generally accepted that the incidence of arteriosclerosis is greater among diabetics than among non-diabetics. With the development since 1912 of the clinical entity of coronary occlusion and resultant myocardial infarction and with the increased interest in diabetes since the introduction of insulin ten years later, much attention has been paid to the relation of diabetes mellitus to coronary sclerosis specifically. For references to early articles on the subject the reader is referred to the bibliographies in articles by Blotner[1] and Root and Sharkey.[2] Subsequent articles on the subject are summarized in Table 1. It is evident from this table that there is a greater incidence of coronary arteriosclerosis in diabetics than in non-diabetics.

One of the striking aspects of this increased occurrence of coronary arteriosclerosis among diabetics is the sex incidence. In the general population the male sex is more often affected, the ratio generally being accepted as 3 or 4 to 1.[9–11] In the diabetic group, however, there is a marked increase in the incidence of coronary sclerosis among females and the ratio therefore decreases. All authors are in agreement on this point although they may differ as to the degree of change. Blotner[1] reported that of thirty-four diabetics with coronary sclerosis twenty-two were female, a ratio of males to females of 1:1.8. This represents a complete reversal of the figures among normals. In a study of coronary disease in non-diabetics Nathanson[3] found a ratio of 3:1 but in a similar study of diabetics[4] the incidence dropped to 1.8:1. Hart and Lisa[12] investigated specifically the sex factor in arteriosclerosis of diabetics. Moderate and severe coronary involvement of persons over forty years of age in a large control group showed a ratio of males to females of 1.11:1; in the diabetic group this fell to 1:1.04.

There has been evidence that the occurrence of arteriosclerosis in diabetics is related to the duration of the disease and not necessarily to the age of the patient. Warren[13] reports that in 484 autopsies on diabetics whose disease had lasted five years or more he has seen only four cases which were free from arteriosclerosis. Arteriosclerosis was present in all the others regardless of age. Shepardson[14] studied the effect of diabetes of five or more years' duration in a group under forty years of age (fifty cases) and found roentgen evidence of peripheral arteriosclerosis in 36 per cent. Rabinowitch, Ritchie and McKee[15] found that among

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diabetics under fifty years of age who had diabetes five years or more cardiovascular disease in general occurred in 85.1 per cent. In a study of 200 diabetics below fifty years of age followed for twenty-five years, Dolger[16] found that every patient developed vascular stances. This figure of 2 per cent is higher than the incidence of diabetes in the general population. Root, Bland, Gordon and White[5] found significant coronary sclerosis (narrowing or occlusion) in 9 per cent of diabetics under the age of forty and in only

TABLE 1

CORONARY ARTERIOSCLEROSIS—OCCURRENCE IN POSTMORTEM STUDIES

Author	Degree of Sclerosis	Age Group	Non-diabetics		Diabetics	
			No. of Cases Studied	Incidence of Coronary Sclerosis Per cent	Incidence of Coronary Sclerosis Per cent	No. of Cases Studied
Blotner[1]	Well marked	Controls: 40–80 Diabetics: 13–85	450	21	45	77
Nathanson[4]	Marked	Over 50 yr.	249	8.2	52.7	74
Root and Sharkey[2]	Occlusive	40 and over	170	13	46.7	157
Root, Bland, Gordon and White[5]	Narrowing with or without occlusion	40 and over	2,310	29	56	316
Lisa, Magiday, Galloway and Hart[6]	Severe	40 and over	2,250	29	46	193
Stearns, Schlesinger and Rudy[7]	Narrowing with occlusion or myocardial fibrosis	Over 40	400	37	74	50
Millard and Root[8]	Occlusion or marked narrowing	.....	2,310	29	68	106

damage regardless of the degree of severity of the disease, insulin requirement, type of diet or degree of control. Chute[17] also reports a high incidence of vascular disease in juvenile diabetics. In view of these findings one would expect a higher incidence of coronary sclerosis in young diabetics than in non-diabetics of comparable age. Unfortunately statistics on coronary arteriosclerosis, specifically, are relatively meager for young diabetics but the available figures generally coincide with the expected. Glendy, Levine and White[18] collected 100 cases of coronary disease in people under forty and found that diabetes was present in two in-

1.3 per cent of non-diabetics in the same age group. Master, Dack and Jaffe[19] analyzed 500 consecutive cases of myocardial infarction. From this study they concluded that diabetes is not a factor in the occurrence of coronary occlusion in the young but nevertheless of their thirty-nine cases under the age of forty two had diabetes, an incidence of 5.1 per cent. Millard and Root[8] report twelve young diabetics who died before the age of thirty-three. Of these five had had diabetes six years or less and showed no arteriosclerosis. Seven had had diabetes fourteen to twenty-one years and all had coronary arteriosclerosis; three had actual

coronary occlusion. These are apparently the same group reported by Root[20] in a separate communication.

Coronary arteriosclerosis is of significance mainly as a cause of clinical heart disease. The increased incidence of coronary sclerosis among diabetics in general, among female diabetics in particular and in the younger age groups has been shown above. It is to be expected then that in all these groups there would be a greater occurrence of the clinical results of coronary sclerosis, namely, angina pectoris, coronary thrombosis and congestive failure.

Angina Pectoris. The reported incidence of angina pectoris among diabetics shows a wide range but nevertheless most reviews are surprisingly consistent. Rabinowitch, Ritchie and McKee[15] found the disability in 1.3 per cent of diabetics in an out-patient clinic while Stearns, Schlesinger and Rudy[7] reported its occurrence in 28 per cent of necropsied diabetics as opposed to 15 per cent in their control group. Blotner,[1] Friedman[21] and Root and Sharkey,[2] however, all report an incidence of 9 per cent. The author has been unable to find any statistics on the incidence of angina pectoris in the general population for purposes of comparison. The incidence parallels the occurrence of coronary artery disease and according to White[11] angina occurred in 11.8 per cent of a series of 3,000 patients with cardiac symptoms or signs. Such a group would naturally have a higher occurrence of angina pectoris than the general population and the figure of 11.8 per cent serves to lend significance to a 9 per cent incidence of this disability among diabetics.

Angina pectoris ordinarily occurs in males and females in a ratio of 3 or 4 to 1.[10,11] Among diabetics, however, the incidence among females increases and the ratio falls. Root and Graybiel[22] found the ratio to be only 1.4:1 among diabetics. Stearns et al.[7] found an incidence of 3.7:1 in their control group and 1:1 among the diabetics. Edeiken[23] who studied out-patients also reports a sex ratio of 1:1.

Other facts stand out as significant. Root and Graybiel[22] report that of those people with angina pectoris the prognosis is worse among diabetics. In the diabetic group which they studied the duration of life from the first anginal attack was two years as opposed to White's unselected cases in which the duration was 3.4 years. Root and Sharkey[2] also point out that the incidence of angina pectoris trebles during the second decade of diabetes.

Coronary Thrombosis. The increased incidence of coronary thrombosis among diabetics is most marked. The papers on this subject are summarized in Table II.

Of further significance are the following facts: Not only is the incidence of coronary thrombosis increased in diabetics but the mortality following the accident is also in-

TABLE II

CORONARY THROMBOSIS—OCCURRENCE IN POSTMORTEM STUDIES

Author	Age of Group Studied	Non-diabetics		Diabetics	
		No. of Cases Studied	Incidence of Coronary Thrombosis Per cent	Incidence of Coronary Thrombosis Per cent	No. of Cases Studied
Enklewitz[24]	50–69	520	16	31	74
Root and Sharkey[2]	40 and over	170	2	19.6	157
Root, Bland, Gordon and White[5]	40 and over	2,310	8	35	316
Lisa, Magiday, Galloway and Hart[6]	40 and over	2,250	22	30	193
Stearns, Schlesinger and Rudy[7]	Over 40	400	23	64	50

creased.[19] In addition, Stearns, Schlesinger and Rudy[7] report that in their series of necropsied diabetics one out of every three had died of acute coronary disease.

The change in sex ratio is also marked. As with coronary sclerosis, coronary thrombosis in unselected cases is three to four times as frequent in males as in females.[19] Among diabetics, however, the ratio falls. In the series of Root and co-authors[5] the incidence of coronary occlusion in male and female diabetics fifty-one to eighty years of age was equal. Stearns et al.,[7] using Schlesinger's injection technic, found coronary occlusion in 31 per cent of male non-diabetics and in 8 per cent of females; in the diabetics it occurred in 68 per cent of men and 61 per cent of women. In other words, in their series coronary occlusion in non-diabetics was four times as frequent in men as in women but among diabetics coronary occlusion increased two-fold in men and eight-fold in women, the incidence in both sexes becoming equal.

Detailed information on angina pectoris in the young is found wanting. More information on coronary occlusion in the young is now becoming available[19,20,25–30,92] but the number of cases reported, exclusive of studies of the armed forces (in whom diabetes is not a factor), is small. Since known diabetes occurs in less than 1 per cent of the population, few statistics are available on coronary occlusion in the young diabetic. The available figures, however, point generally to an increased incidence of coronary thrombosis. Of Durant's[30] seven cases of coronary thrombosis in people thirty-five years of age or less one was diabetic. Master et al.[19] report thirty-nine cases of coronary thrombosis in patients under forty years of age; two (5.1 per cent) had diabetes. Among Stryker's[26] nine infants and children under the age of seventeen who had coronary occlusion none were diabetics. Goodson and Willius[92] make no mention of diabetes in their report of thirty cases of coronary thrombosis in persons less than forty years of age. If all the above mentioned series are totalled (85), however, the incidence of diabetics (3) among them is higher than that in the general population.

Congestive Failure. There have been few reports on the incidence of congestive failure among diabetics. This is readily understandable when it is realized that congestive failure may result from any one of several causes, one or more of which may be present in a single diabetic at the same time. Coronary sclerosis alone, coronary thrombosis with myocardial infarction and hypertension may each give rise to heart failure and are frequently present in diabetics. The incidence in diabetics of the specific etiologies has interested investigators more than the occasionally resulting clinical picture of cardiac insufficiency. Root and Sharkey[2] merely state that in their post-mortem study congestive heart failure was infrequent; when it occurred, it usually followed coronary thrombosis. This is in contrast to other available figures. Friedman[21] found cardiac decompensation in 8 per cent of 120 living diabetics, and Stearns et al.,[7] reviewing the protocols of fifty necropsied diabetics, found that congestive failure had been present in twenty-seven, an incidence of 58 per cent.

CAUSES OF CORONARY ARTERIOSCLEROSIS IN DIABETES

The etiology of the increased incidence of coronary arteriosclerosis among diabetics is unknown. It is believed by some that diabetes is simply another clinical manifestation of arteriosclerosis and that an increased occurrence of arteriosclerosis anywhere in the body is to be expected. The weight of statistical evidence, however, points to the increase in arteriosclerosis in diabetics as the result rather than the cause of the disease. Two factors have been implicated as at least contributing to the increased incidence, hypertension and hypercholesterolemia.

Hypertension. References to early discussions of the blood pressure in diabetes are contained in Major's[31] article. Opinion was divided as to whether or not diabetics showed an increased incidence of hypertension. According to Major the blood

pressure was only slightly higher in diabetics than in control series but was definitely higher in diabetic women in the older age groups. Edeiken[23] reported hypertension in 38 per cent of 100 diabetics studied clinically, the women being affected twice as often as the men. All those with high blood pressure were over fifty years of age. Bell and Clawson[32] found hypertension relatively uncommon in necropsied diabetics under forty years of age but in persons over the age of fifty high blood pressure was 2.7 times as frequent in diabetics as in nondiabetics. Among the older diabetics hypertension occurred in 42.5 per cent, which is very close to the figure of 44 per cent found by Enklewitz[24] in his postmortem study. Other reports show an even higher incidence. Transient and permanent high blood pressure occurred in 56 per cent of Friedman's[21] clinical series and in 53 per cent in Root and Sharkey's postmortem study.[33] Even more startling is White and Waskow's[34] finding of hypertension in 40 per cent of 200 diabetics, 5 per cent of whom were under forty years of age. Of recent investigations only Nathanson[4] has found a relatively low (15 per cent) incidence of hypertension in diabetics, but even this figure is higher than that found in the general population.[35]

Associated Findings in Coronary Arteries. The increased incidence of hypertension in diabetics is reflected in the coronary arteries. In Blotner's[1] series of necropsied diabetics high blood pressure was present in 43 per cent of those with coronary arteriosclerosis. Root and Graybiel[22] found it in 52 per cent of 210 diabetics with angina pectoris. According to Root and Sharkey[2] coronary thrombosis is three times as frequent in diabetics with hypertension as in those without. Likewise, Stearns et al.[7] find that among diabetics angina pectoris and deaths due to acute coronary disease and congestive failure are more common in the presence of hypertension.

Hypercholesterolemia. It is beyond the scope of this review to discuss hypercholesterolemia in relation to the pathogenesis of coronary atherosclerosis. Some mention of the clinical association is in order, however. Cholesterol has long been implicated in the causation of atherosclerosis. The substance is found in high concentration in the plaques of atherosclerosis, and atherosclerosis is found to be of high incidence in the presence of hypercholesterolemia. The inference is that a high blood level of the sterol results in high incidence of intimal sclerosis. Such an association of events does occur in rabbits,[36] chickens[37,38] and dogs.[39] Conversely, the administration of decholesterolizing agents such as choline, methionine, potassium iodide and thyroid results in a decrease in atherosclerosis.[40,41]

The transfer of such experimental work to humans presents problems. The blood cholesterol levels of normal man is not readily elevated by diet. The administration of a high cholesterol diet to a large group for a long period of time would be practically difficult and perhaps eventually dangerous. Investigation of the state of the coronary arteries in patients who have disease associated with hypercholesterolemia, however, yields some of the desired information. In xanthomatosis which is characterized by high blood cholesterol the incidence of coronary sclerosis is extremely high. Muller[42] found that of seventy-six patients who had hereditary xanthomatosis sixty-eight (90 per cent) had angina pectoris and/or myocardial infarction. Engelberg and Newman[43] report six cases of xanthomatosis in young adults (ages thirty-one to forty-eight), all of whom had angina pectoris and/or myocardial infarcts. Similar although perhaps less direct information is obtained from the finding of higher blood cholesterol levels in cases of uncomplicated coronary sclerosis than in normals.[29,44–46]

CARDIAC COMPLICATIONS OF DIABETIC ACIDOSIS

Cardiovascular Collapse. Coronary arteriosclerosis in the diabetic is a complication of the chronic disease. Diabetic acidosis, the "acute" disease, also has its cardiovascular complication. Even in the absence of disease of the coronary arteries diabetic acidosis

may be associated with the type of circulatory failure commonly known as shock. The high frequency and importance of this complication is attested by many authors.[47–53] The clinical picture is familiar: tachycardia, low blood pressure, decreased pulse pressure, cold skin, depressed sensorium. Such shock often persists in the presence of levels of blood sugar, ketones and CO_2 combining power that are approaching normal. In fact, Nicholson and Branning[54] report that of twenty-two treated but fatal cases of uncomplicated diabetic acidosis there were five who had normal blood sugar and CO_2 combining power and who showed no lesions at autopsy. All died in collapse. The complication is of grave importance because of the concomitant increase in mortality. Rabinowitch, Fowler and Bensley[49] found that the mortality in their cases of diabetic acidosis was 11.5 per cent if the systolic blood pressure was 90 mm. Hg or over; it was 53.8 per cent if under 90 mm., almost five times as great. Collen[52] reported that mortality for those with blood pressure 90 mm. or over averaged 27.6 per cent and for those under 90 mm. 75 per cent, almost three times as great. Danowski, Winkler and Peters[53] found that in recovered cases of diabetic acidosis the incidence of vascular collapse had been 20 per cent; in fatal cases, 85 per cent. Collen's study[52] is of further interest. He demonstrates that the diastolic pressure shows a much closer quantitative relationship to percentage mortality than the systolic blood pressure; also, if the pulse pressure is less than 20, the mortality is 92.8 per cent. The situation may be summarized by quoting from Danowski and his co-workers[53] who state " . . . that some measure of peripheral vascular collapse is commonly found in severe diabetic acidosis and that its persistence is the usual reason for failure to recover from acidosis."

Peters, Bulger and Eisenman[50] showed that diabetic acidosis is associated with dehydration and hemoconcentration. Chang, Harrop and Schaub,[57] using the carbon monoxide method, demonstrated that the dehydration results in a marked decrease in the circulating blood volume, the loss of volume being chiefly a decrease in plasma; the cell volume remains intact. It was subsequently shown[50,51,53,58–60] that not only is water lost in diabetic acidosis but that sodium and chloride ions are also lost in large amounts and must be quickly replaced for the prevention or treatment of circulatory collapse. Further work[50,53,61] has demonstrated the need for the administration of protein in addition to electrolytes and water in the treatment of the more severe cases of shock. More recently Howarth, McMichael and Sharpey-Schafer[62] have shown that the low blood pressure of diabetic acidosis is due to a marked decrease in total peripheral resistance; cardiac output remains normal. Their work suggests that an effective, long-lasting vasoconstrictor agent would be the medication of choice in the treatment of diabetic shock.

Hypopotassemia. Recently it has been shown that potassium, too, is of clinical importance in diabetic acidosis and that depletion of this electrolyte often has cardiac manifestations. Potassium is lost from the body in several ways. First, there is increased excretion of the substance in diuresis due to any cause[63] and the diuresis associated with marked glycosuria results in loss of the electrolyte in patients going into diabetic acidosis.[59] During the height of dehydration, which corresponds to the period just before treatment of the acidosis, loss of potassium is noted in the cells.[63,64] The serum level remains approximately normal,[64] however, and there are no signs of potassium deficiency. The second manner of potassium loss is a relative one. Treatment consists, in part, of administration of large amounts of water. If potassium is not given in conjunction with the water, the amount of electrolyte remaining in the body at the height of acidosis is much diluted by the rehydration of treatment with resulting marked fall in the concentration of serum potassium.[64,65] A third way in which potassium is lost is thought by some to be due to a specific effect of insulin. Several

authors[59,66–68] have reported a fall in concentration of serum or plasma potassium following the injection of insulin. More recent work[65,69,70] suggests that this may be related to the passage of the electrolyte into muscle or liver in association with increased glycogen formation.

As seen above, it is with treatment of acidosis that serum potassium concentration falls. It is therefore not on admission but following institution of therapy that the results of potassium deficiency become apparent in patients with diabetic acidosis. The best known cardiac manifestation of hypopotassemia is abnormality of the electrocardiogram. In the presence of low serum potassium the latter shows abnormal increase in the P-R interval, depression of the S-T segment, prolongation of Q-T (electrical systole) and low to inverted T waves. These findings have been reported in association with the hypopotassemia of periodic paralysis,[71,72] chronic nephritis[73] and other causes.[74] Bellet and Dyer[75] were the first to report consistent electrocardiographic change associated with diabetic acidosis. Although the authors did not correlate the changes with potassium concentration, the changes are those of hypopotassemia and they noted that the changes occurred not during coma but twenty-four hours later (i.e., after institution of therapy and clinical improvement of the patient). Stewart, Smith and Milhorat,[71] Holler[76] and Martin and Wertman[77] have correlated these changes with the low serum potassium of treated diabetic acidosis. The latter report that of all the electrocardiographic changes found only low T waves show a high correlation with low serum potassium.

Not only is there alteration of electrical conduction in the myocardium but also new foci for the origin of the stimulating impulse appear. Bellet and Dyer[75] reported temporary auricular flutter and auricular and ventricular premature beats in some of their patients. Frenkel, Groen and Willebrands[78] report the appearance of "irregular pulse" in association with low serum potassium level with reappearance of normal rhythm following the administration of potassium. Nicholson and Branning[54] suggest that low serum potassium may be the cause of death from collapse that occurs in some patients with diabetic acidosis whose blood sugar and CO_2 combining power have become normal following usual therapy.

EFFECTS OF INSULIN

Hypoglycemia. It must be pointed out that although the administration of insulin is necessary for the treatment of many diabetics, overdosage of the hormone in these patients may result in cardiovascular complications. Hypoglycemia may cause angina pectoris,[79,80,82,90] myocardial infarction,[81] congestive failure,[94–96] changes in the electrocardiogram[81–85,90,93,96–100,103,104] and changes in rhythm.[82,84,85,100,101] Hypoglycemia has also been associated with the appearance of other changes of the circulation such as increase or decrease in heart rate,[55,81,82,86,93,96] increase or decrease in blood pressure,[82,93,102] increase in venous pressure,[81] increase in pulse pressure,[84,86] the development of an abnormal heart murmur[55,84] and increase in heart size.[84]

The explanation for these changes is not yet clear. The obvious thought is that with hypoglycemia there is concomitant marked loss of myocardial glycogen and that this gives rise to the cardiac abnormalities. Cruickshank,[87,88] however, showed that the diabetic heart has a much greater than normal glycogen content in the presence of hyperglycemia and that with the administration of insulin the glycogen content falls only to normal. Even in the presence of very low blood sugar insulin conserves the glycogen stored in the heart. Other facts also suggest that the low blood sugar alone is not the cause of the cardiovascular changes observed in hypoglycemia. There is no correlation between clinical findings and the blood sugar level;[83] the changes seen are not necessarily, or promptly, reversed by the administration of glucose.[83,84,96] Probably the most tenable theory of the causation of cardiovascular changes in hypoglycemia is that the low blood sugar causes increased

discharge of adrenalin. Cannon, McIver and Bliss[89] demonstrated in cats that even the completely denervated heart responds to hypoglycemia by an increase in rate if the adrenals are intact. If the adrenals are removed or one is removed and the other denervated, insulin hypoglycemia causes no increase in rate. It is well known that the injection of adrenalin into the normal human produces many of the clinical signs of hypoglycemia (tachycardia, pallor, tremor, increased blood pressure). Furthermore Gilbert and Goldzieher[81] have demonstrated that the usual circulatory changes taking place in insulin hypoglycemia do not occur if prostigmin is administered at the same time as the insulin.

Whatever the mode of causation, the danger of insulin overdosage is appreciable. Ernstene and Altschule,[86] working with normal humans, showed that insulin hypoglycemia results in increased heart rate, increased pulse pressure and increased minute volume output, i.e., cardiac work is greater. Such added work gave rise to no difficulty in their normal subjects but they suggest that among diabetics, a large percentage of whom have coronary arteriosclerosis, such added work could readily result in cardiac insufficiency and /or angina pectoris. For the same reason Gilbert and Goldzieher[81] believe that close control of elderly diabetics is not desirable and Smith,[95] citing the clinical complications of the treatment of diabetes, states that " . . . to use insulin to procure exact control of the diabetes in patients with additional heart disease is to court disaster."

Some of the effects of insulin may be bothersome even in the absence of marked hypoglycemia. It is common experience in the treatment of diabetics that many patients simply feel better with slight glycosuria than with excellent control. The cardiac symptoms (tachycardia, palpitation, substernal pain, shortness of breath) associated with spontaneous hypoglycemia are very distressing[91] and such symptoms occur in diabetics with only slight insulin overdosage. It is interesting to note that some of them (palpitation, precordial pain) have also been reported in patients who were given therapeutic amounts of insulin and who did not have hypoglycemia.[82]

SUMMARY

1. The cardiac complications of diabetes mellitus are discussed under the following headings: (1) coronary arteriosclerosis, (2) diabetic acidosis and (3) hypoglycemia.

2. There is a higher incidence of coronary arteriosclerosis and its clinical manifestations among diabetics than among non-diabetics. This higher incidence is more marked in women. The duration of the diabetes is probably the greatest single factor in the occurrence of coronary arteriosclerosis.

3. Cardiovascular collapse occurs frequently in diabetic acidosis. Prevention and treatment of such shock consists of the administration of adequate amounts of water, sodium chloride, protein and potassium.

4. Insulin reactions are associated with cardiac complications particularly in the older age groups. Completely aglycosuric control of elderly diabetics by the use of insulin is not desirable.

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Seminars on Antibiotics

Chloramphenicol (Chloromycetin) in the Treatment of Infectious Diseases*

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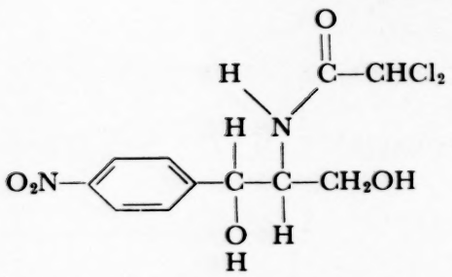
CHLORAMPHENICOL is one of the important recent additions to the group of antibiotics of proved clinical value. It is effective against a wide variety of infectious agents in the laboratory and on the ward. The purified crystalline form of the antibiotic, obtained from the fermentation products of the mold Streptomyces venezuelae, was used in most of the early laboratory and clinical studies. The active material was shown to have a relatively simple chemical structure and shortly thereafter it was produced synthetically on a practical basis and made available for clinical use.

HISTORY OF DEVELOPMENT AND SYNTHESIS

During the course of a systematic search for new antibiotic agents a Streptomyces species which possessed antibiotic properties against several bacterial organisms was isolated by Dr. Paul R. Burkholder of the Osborn Botanical Laboratory at Yale University from a sample of soil collected in Venezuela. This culture, together with a number of others which showed promise, was given to the Research Laboratories of Parke, Davis and Company. The results of a series of integrated investigations by workers in the Research Laboratories[1,2,3] indicated that (1) a substance with marked antibiotic activities was readily obtained from filtrates of Burkholder's organism (which was subsequently named Streptomyces venezuelae) when grown in large tanks, (2) the antibiotic activity of the filtrates was attributable to a stable substance obtained in crystalline form and named Chloromycetin, (3) the crystalline antibiotic was well absorbed when administered orally to laboratory animals and (4) the new material was of low toxicity for animals. While the early work on the spectrum of organisms affected by the new antibiotic was devoted primarily to a study of bacterial species, exploratory studies with Rickettsia prowazeki suggested that this rickettsial agent might also be susceptible.[1] At this point a third group of investigators, those at the Army Medical Department Research and Graduate School, began a series of studies designed to determine the efficacy of the antibiotic against viral and rickettsial agents.[4,5,6] These focused attention on the marked antirickettsial properties of the antibiotic and on the low toxicity of Chloromycetin for man.[7] The results of laboratory studies stimulated clinical trials in which patients with rickettsial diseases were treated with the newly recognized substance.

Crystalline Chloromycetin obtained by the fermentation process provided the biochemists in the Research Laboratories at Parke, Davis and Company with suitable material for studies on the chemical structure of the antibiotic. Chloromycetin proved to be a rather simple substance; according to Rebstock, Crooks, Controulis and Bartz[8] its structural formula is:

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The authors state, "Chloramphenicol is, so far as we know, the first naturally occurring compound which contains a nitro group or which is a derivative of dichloracetic acid." These workers proved the validity of their formula by synthesizing the material and demonstrating that this substance had all of the physical and chemical properties of the natural antibiotic obtained by the fermentation process.[9] The synthesized drug was promptly shown to be as efficacious in the treatment of experimental animals and of patients as was the natural substance obtained from the mold.[10]

The generic name chloramphenicol was given to the new antibiotic and the term Chloromycetin designated as a trade mark.

EFFECT OF CHLORAMPHENICOL ON MICROBIAL AGENTS

Rickettsiae and Viruses. Chloramphenicol was originally recognized and developed because of its *in vitro* antibacterial effects. However, its antirickettsial properties rapidly assumed paramount importance. It will be recalled that in 1947 no highly satisfactory chemotherapeutic agent existed for the treatment of the rickettsial diseases of man.[11]

Viruses and rickettsiae are obligate intracellular parasites which multiply only in the presence of living cells. Past experience has shown little correlation between the capacity of various substances to inactivate these microbial agents *in vitro* with their capacity to inhibit growth of the agents *in vivo*. Therefore, in our screening program no attempt is made to determine *in vitro* destruction of viruses or rickettsiae until after a given substance has shown promise *in vivo*. Thus initial studies with new substances are performed as chemoprophylactic or chemotherapeutic tests using infected rodents or embryonated eggs.

Table 1 summarizes the available information on the inhibitory effect of chloramphenicol on the growth of a number of rickettsiae and viruses. Since the tabular data are derived from *in vivo* experiments which vary somewhat in design from one infectious agent to another, it is not feasible to express the degree of inhibition numerically. It is apparent from the table that all of the rickettsial agents which have been tested with chloramphenicol are markedly inhibited *in vivo*. Members of the psittacosis-lymphogranuloma venereum group of viruses, which are so closely related to the rickettsiae that they are classified as members of the family Chlamydozoaceae of the order Rickettsiales Gieszczykiewicz in the sixth edition of Bergey's "Manual of Determinative Bacteriology," are also markedly inhibited by this antibiotic. In sharp contrast, none of the other viruses is affected.

Certain of the experimental rickettsial infections appear to respond more readily to chloramphenicol than others. For example, when tested in embryonated eggs a significant prolongation of life of the embryos is obtained when 0.0625 mg. of drug is injected on one occasion into eggs infected with the agent of spotted fever, whereas 0.5 mg. is required to obtain a significant effect in embryos infected with the agent of Q fever.[6] In such experiments as these the prolongation of life of embryos is equally great whether the drug is administered immediately before inoculation of infectious material or a day or so later. Even within a given species of rickettsiae certain strains may be more susceptible to chemotherapy than others. This is illustrated by the response of groups of mice infected with the Karp and the Seerangayee strains of R. tsutsugamushi. Daily administration of 2.5 mg. of chloramphenicol per mouse for twelve days after inoculation results in survival of all animals infected with the Karp organism and in death of practically all animals infected with the Seerangayee strain. Prolongation of treatment for twenty

days permits survival of practically all mice infected with Seerangayee. It should be mentioned that in such experiments as these, death occurs in infected untreated animals during the third week after inoculation.[6]

Chloramphenicol has no direct rickettsiocidal effect when tested *in vitro* in concentrations of 1250 μg/ml. against either R. tsutsugamushi or the virus of psittacosis. Furthermore, in at least several of the experimental infections which are benefited by chloramphenicol the therapy does not result in sterilization of tissues. This has been carefully studied in mice infected with R. tsutsugamushi. Here viable organisms may be recovered from the spleens of infected mice 100 days after inoculation despite the fact that the animals have received a full therapeutic dose of 2.5 mg. per day during the entire period of time.[6] With certain of the other agents, i.e., R. rickettsii and R. akari, preliminary data suggest that actual sterilization of the tissues may occur in some of the animals which recover from infection. However, it may be that autosterilization occurs rather promptly in experimental animals which survive infection with these particular agents. The subject of mode of action of chloramphenicol will be discussed in a general way in other sections of this review. Suffice it to say here that in scrub typhus infections in man and mouse chloramphenicol does not "cure" the patient; the antibiotic suppresses growth of the rickettsiae and permits the individual to develop his immune processes and thus to recover from the disease.

TABLE I

INHIBITORY EFFECT OF CHLORAMPHENICOL ON GROWTH OF RICKETTSIAE AND VIRUSES IN LABORATORY ANIMALS

Agent and Reference	Inhibition
Rickettsiae:	
Epidemic typhus[1,4]	Marked
Murine typhus[4]	Marked
Scrub typhus[4]	Marked
Rocky Mountain spotted fever[4]	Marked
Rickettsialpox[4]	Marked
Q fever[6]	Marked
Viruses:	
Lymphogranuloma venereum[4,5]	Marked
Psittacosis[4,5]	Marked
Variola-vaccinia[4,12]	None
Influenza A, A′ and B[4,12]	None
Mumps[12]	None
Lymphocytic choriomeningitis[14]	None
Eastern equine encephalomyelitis[14]	None
Western equine encephalomyelitis[14]	None
St. Louis encephalitis[3]	None
Japanese encephalitis[4]	None
Rabies[3]	None
Poliomyelitis (Lansing, Yale-SK)[13]	None
Mouse encephalomyelitis[13]	None
Distemper[12]	None
Newcastle disease[3]	None
Chick bronchitis[12]	None
Laryngotracheitis[12]	None

TABLE II

IN VITRO SENSITIVITY OF BACTERIA TO CHLORAMPHENICOL*

Organism	Inhibiting Concentration μg/ml.†
Alcaligenes fecalis	1.0
Bacillus anthracis	1.0–5.0
Brucella abortus	2.5–10
Clostridia (genus)	>500
Corynebacterium diphtheriae	0.5
Diplococcus pneumoniae	1.0–2.5
Escherichiae coli	2.5
Hemophilus influenzae	3.6‡
Hemophilus pertussis	0.2
Klebsiella pneumoniae	0.5–2.5
Malleomyces mallei	40
Mycobacterium tuberculosis	6–12
Neisseria meningitidis	2.5
Pasteurella (genus)	0.2–2.5
Proteus (genus)	1–25
Pseudomonas (genus)	10–100
Salmonella enteritidis	0.7–2.5
Salmonella paratyphi	0.7
Salmonella schottmuelleri	0.5–2.5
Salmonella typhosa	1–5.0
Shigella dysenteriae	0.7
Shigella paradysenteriae	0.5–2.5
Shigella sonnei	2.5–5.0
Streptococcus pyogenes (hemolyticus)	0.7–2.5
Vibrio comma	1.0

* Information from McLean et al.[12]

† Minimum inhibiting concentrations were determined on the basis of complete inhibition of growth of the designated organism in fluid medium at eighteen hours.

‡ From Dr. T. E. Woodward, personal communication.

Bacteria. Chloramphenicol has an inhibitory effect on the growth *in vitro* of a wide range of bacteria. A number of the early publications contained lists of organisms with their susceptibility to chloramphenicol as determined by one of several methods.[1,3,15,16] The recent report by Mc-

Lean and his associates[12] presents the most extensive single list currently available, moreover all organisms mentioned were tested by a single method. Information contained in Table II has been taken almost entirely from this source.[12] The tabular data indicate the minimum concentration of chloramphenicol required to cause complete inhibition of growth in fluid medium of a number of bacterial species which are pathogenic for man.

Inspection of Table II reveals a preponderance of gram-negative bacteria. Chloramphenicol does indeed possess considerable activity against gram-negative organisms. While inhibition of growth of staphylococci and streptococci is obtained, the concentrations required to affect these organisms are far in excess of the effective concentrations of penicillin. Such information as that given in Table II is of interest to the physician early in the work with a new antibiotic since it supplies leads which may be of value in experimental chemotherapy studies in animals and in man. In fact, demonstrable effectiveness *in vitro* of a new antibiotic against a number of bacteria of medical importance is usually a prerequisite for continued general interest in that substance. However, unless such an antibiotic possesses many other satisfactory characteristics, the new substance remains a matter of academic interest to a few laboratory workers.

It would be pertinent in a review of this type to present extensive experimental evidence of the chemotherapeutic effect of chloramphenicol against a number of experimental bacterial infections in animals. While a certain amount of such information is available, it is extremely limited. This is due in part to the fact that early in its history chloramphenicol was used in the treatment of patients with rickettsial disease, and subsequently was employed in bacterial infections of man without waiting for the results of the usual laboratory experimentation. This is illustrated in the successful treatment with chloramphenicol of patients suffering from typhoid fever.[17] An even more extreme example is found in its use in the satisfactory treatment of acute gonorrheal urethritis in the male;[18] here laboratory data are still not available on the *in vitro* effect of chloramphenicol on Neisseria gonococcus.

The work of Youmans and his colleagues on the tuberculostatic action of chloramphenicol in mice is encouraging and deserves to be extended, particularly since the blood levels obtained in the treated mice were well below those which can be produced readily in human beings.[19] Gauld and his co-workers[20] demonstrated the efficacy of chloramphenicol in mice inoculated with Vibrio comma. However, they pointed out the difficulties which would accompany chemotherapy of cholera in man and suggested that its principal use in this infection might be as a prophylactic agent during an epidemic.

Woodward and his co-workers[21] found that chloramphenicol had little beneficial effect in mice treated for three days after infection with Pasteurella tularensis. Under these same conditions streptomycin gave somewhat more satisfactory results but aureomycin was superior to the other two antibiotics. Smith and his colleagues make the following statement:[3] "Exploratory experiments, using small numbers of mice infected intraperitoneally with lethal doses of virulent *Klebsiella pneumoniae* (type A), *Shigella paradysenteriae* (Flexner), *Shigella paradysenteriae* (Sonne), *Diplococcus pneumoniae* (type I), *Streptococcus hemolyticus*, and *Streptococcus viridans* and treated subcutaneously with chloromycetin in 20 per cent propylene glycol, streptomycin sulfate, or penicillin G, showed that chloromycetin was qualitatively similar to streptomycin but quantitatively inferior in protective action."

The results obtained when mice were infected with Salmonella typhimurium and treated with chloramphenicol were considered by Seligmann and Wassermann[22] to be discouraging. It is to be noted that their treated mice survived during the relatively short period of therapy but subsequently died. This brings up several points which

are worth mentioning at this time. In the first place, chloramphenicol may be highly bacteriostatic for a given organism but almost completely lacking in bactericidal power for the same organism. Thus concentrations of 1000 μg/ml. in fluid media do not kill S. typhosa.[17b] This is similar to the observation described earlier in which chloramphenicol had no *in vitro* rickettsiocidal activity against R. tsutsugamushi. With these two agents, at least, recovery of the individual must depend upon the development of immunity in the infected host since the antibiotic merely suppresses growth of the organisms. The situation in mice infected with S. typhimurium may be similar to that in man infected with S. typhosa. In the latter instance, if relapses are to be avoided, chloramphenicol therapy must be continued for longer than eight days.[23]

Fungi. The majority of the fungi which have been examined are not affected by chloramphenicol. McLean and his associates[12] tested twenty-one strains from eleven genera of pathogenic fungi and sixteen strains from nine genera of non-pathogenic fungi. Growth of two representatives from the first group, namely, Actinomyces bovis and Nocardia asteroides, both of which are causal agents of actinomycosis, were completely inhibited by concentrations of 5 to 20μg/ml. The remaining organisms in both groups were not inhibited appreciably by concentrations of 1000 to 2500 μg/ml.

Spirochetes. Experimental infection in rabbits caused by Nichols strain of Treponema pallidum was not affected by daily doses of 25 mg. of chloramphenicol per Kg. of body weight. Double and quadruple this amount cleared the lesions of spirochetes and permitted healing temporarily.[3] These preliminary results suggest that chloramphenicol does not compare favorably with penicillin in the therapy of experimental syphilis.

Spirochetes of relapsing fever, Borrelia novyi and B. recurrentis, were immobilized by chloramphenicol *in vitro* and infection in mice with the first organism was suppressed appreciably by small doses of the drug.[3,12]

Protozoa. Chloramphenicol had no appreciable antimalarial effect when tested in ducks and chickens infected with Plasmodium lophurae.[3] High concentrations of the drug did not affect Trichomonas foetus but in certain culture media reduced the number of Endamoeba histolytica. The latter observation in itself may be of little importance since the result may have been an indirect one involving the bacteria which occur in the cultures and serve as a nutrient supply for the ameba. Of greater significance, however, is the observation that an appreciable clearing of infection occurred in rats and dogs with experimental amebiasis which were given large doses of drug.[12]

Development of Resistance by Micro-organisms. McLean and his co-workers[12] have shown that resistant variants can be developed from a number of species of bacteria which were originally susceptible to chloramphenicol. This was done in the usual manner, i.e., growing the culture in increasing concentrations of the antibiotic.

Neither the experience of these workers nor that in our laboratory[6] has presented evidence that drug-resistant strains of rickettsiae can be developed under experimental conditions.

It is noteworthy that clinical experience in the treatment of typhoid fever and scrub typhus has provided no indication that resistant strains make their appearance in treated patients.[17,24] Thus it would appear that this phenomenon may be expected to be of little importance to the physician.

LABORATORY METHODS FOR DETERMINATION OF CHLORAMPHENICOL LEVELS

Chloramphenicol is an extremely stable compound. It is unaffected over the pH range from 2-9 or by boiling in distilled water for a number of hours.[2] The solubility of the neutral, white crystalline drug in distilled water is 0.25 per cent. Solutions of this concentration may be kept for months at icebox temperatures for use as the standard in assays for chloramphenicol. Solutions containing less than 1.0 mg. per ml. deteri-

orate after a few days or weeks of storage in the refrigerator.

Bioassay. A number of the methods which have proved suitable for assaying other antibiotics have been used with chloramphenicol.[1,3,12,15,16,19] At the Army Medical Department Research and Graduate School a modification of the turbidimetric method of Ehrlich and his associates[3] has been used most extensively. In this technic the amount of crystalline drug in a known standard solution which is required to produce 50 per cent inhibition of growth of Shigella sonnei is compared spectrophotometrically with the inhibiting capacity of varying dilutions of the unknown material. The method determines the amount of biologically active chloramphenicol and is satisfactory for estimating the drug levels in serum, urine and spinal fluid and, with some slight modifications, milk and bile.

Chemical Method. The chemical method for determining chloramphenicol, as described by Glazko and his associates,[25] is based on the reduction of the nitro group of the chloramphenicol molecule to a primary amine (this is effected by heating with zinc dust) followed by diazotization and coupling. The color produced by this reaction is proportional to the concentration of chloramphenicol. In essence, after conversion to the primary amine the method is essentially identical with the procedure of Bratton and Marshall for determination of sulfonamide. As would be expected under these circumstances the presence of sulfonamides interferes with the test.

About 10 per cent of the chloramphenicol administered to human beings and dogs is excreted in the urine in the active form and is detectable by bioassay. In dogs most of the administered chloramphenicol appears in the urine in the form of inactive nitro compounds which, like the active substance, react in the chemical determination for chloramphenicol. In human beings most of the chloramphenicol is excreted in an inactive conjugated form, probably as the monoglucuronide.[25]

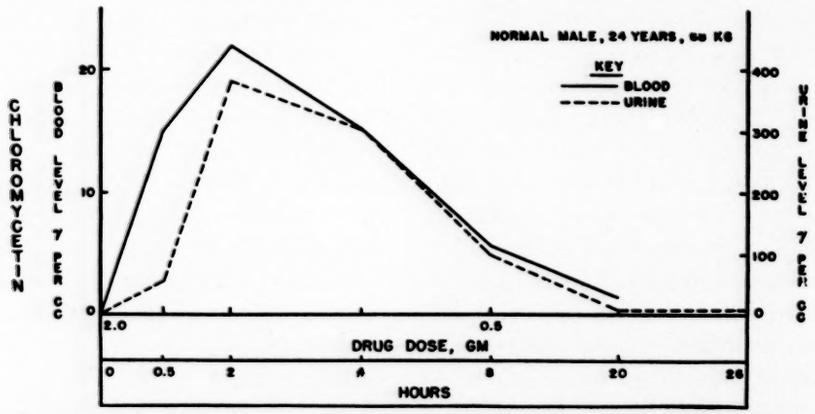


FIG. 1. Blood and urine levels of chloramphenicol following a 2.0 Gm. oral dose. Determinations were by the bioassay method. (Reproduced from *Proc. Soc. Exper. Biol. & Med.*, 68: 9–12, 1948.[7])

Since relatively small amounts of the degradation forms of the drug are present in blood and spinal fluid, the chemical determination gives a close approximation of the amount of biologically active antibiotic which is present. On the other hand, the occurrence of large amounts of degradation products in the urine interferes with the chemical estimation of the amount of active drug.

Levels of Chloramphenicol in Body Fluids of Man. Figure 1 illustrates the levels of chloramphenicol attained in the blood and urine of a normal person following the oral administration of a single 2.0 Gm. dose of drug. These data, obtained by bioassay, indicate that the drug is rapidly absorbed

from the gastrointestinal tract and reaches appreciable levels in both blood and urine within one-half hour.[7] The maximal blood levels, which are usually of the order of 20 to 40 μg/ml. following a 2.0 Gm. dose and 40 to 60 μg/ml. after a 4.0 Gm. dose, are reached within one to three hours. The values gradually decline and no detectable antibiotic is found at eighteen to twenty-four hours. The levels of active material in the urine are appreciably higher than in the blood but the rise and fall follow the same general pattern. The amounts of chloramphenicol in the spinal fluid, bile and milk of human beings are about half those found simultaneously in the blood.[17b,24b]

CLINICAL USE OF CHLORAMPHENICOL

Rickettsial Diseases

Typhus Fevers (Epidemic, Murine and Scrub). The early laboratory studies indicated that chloramphenicol might be of value in the treatment of rickettsial diseases. Since satisfactory therapeutic measures were particularly needed for this group of infections, the first clinical trials of the new drug were made with patients suffering from typhus fever during the winter of 1947 and 1948 in Bolivia[26] and in Mexico.[27] These initial observations provided highly encouraging results but both tests left something to be desired. Although carefully studied the Mexican patients with epidemic and murine typhus were few in number. On the other hand, while a larger group of patients was treated in Bolivia during an epidemic of louse-borne typhus, facilities were not available for the extensive study of individuals. Additional results with chloramphenicol in the treatment of patients with epidemic and murine typhus have not been reported, nevertheless, these two preliminary trials have received much indirect support from the results of therapeutic studies with this antibiotic in patients with two other rickettsial diseases, i. e., scrub typhus and Rocky Mountain spotted fever. There is little point in discussing the therapeutic regimens employed in the first groups of typhus fever patients who were treated with chloramphenicol since subsequent studies have provided information which should now be applied to these two diseases.

The work in Malaya of the U. S. Army Scrub Typhus Research Team on the treatment of tsutsugamushi disease provided conclusive evidence of the efficacy of chloramphenicol in the therapy of rickettsial diseases.[24] The data on the first thirty patients with naturally acquired scrub typhus who received this new antibiotic are summarized in Table III.

TABLE III
SCRUB TYPHUS PATIENTS
KUALA LUMPUR, 1948*

	Treated	Untreated
No. patients	30 23 males 7 females	19 16 males 3 females
Day after onset R_t begun	3 to 11, av. 6.2	
Last febrile day of illness	4 to 12, av. 7.4	12 to 31 av. 17.1
Duration of fever after R_t begun (hr.)	6 to 96, av. 31.8	
Day after onset discharged from hospital	14 to 28, av. 17.8	17 to 51 av. 29.9
Complications	0	1 parotitis 1 pneumonia
Deaths	0	1 17th day
Month of onset	March–Sept.	Feb.–June

* Reproduced from Smadel, Woodward, Ley and Lewthwaite.[24b]

The typical response of a treated patient in this series is illustrated graphically in Figure 2. All of the Malayan patients received an initial oral dose of 3.0 to 4.0 Gm. of chloramphenicol. This was followed by 0.25 Gm. amounts at intervals of two to three hours for a varying period of time. The first patients were treated over a period of five or six days but subsequent observations showed that such long periods of therapy were unnecessary. Indeed, a single oral dose of 3.0 to 4.0 Gm. of drug was sufficient to control the disease in a number of patients who received this regimen. However, the ultimate practice

was to give an initial loading dose of 3.0 or 4.0 Gm. and follow this with 0.25 Gm. every three hours during the succeeding twenty-four hours.

Chloramphenicol has been used prophylactically in human beings exposed to scrub typhus. It has been shown that daily oral doses of 1.0 Gm. or weekly doses of 4.0 Gm. are sufficient to suppress clinical evidence of disease in volunteers who were exposed in hyperendemic areas of scrub typhus in Malaya. When prophylaxis was continued for only two weeks after the end of exposure, scrub typhus developed in the volunteers about a week after the last prophylactic dose of drug.[28] However, when the regimen was continued for four weeks after the last exposure, none of the volunteers subsequently developed clinical disease.[29] Here again the evidence indicates that chloramphenicol is rickettsiostatic but not rickettsiocidal. It would appear that suppression must be maintained long enough for the individual to develop immunity if he is to remain asymptomatic when the drug is discontinued.

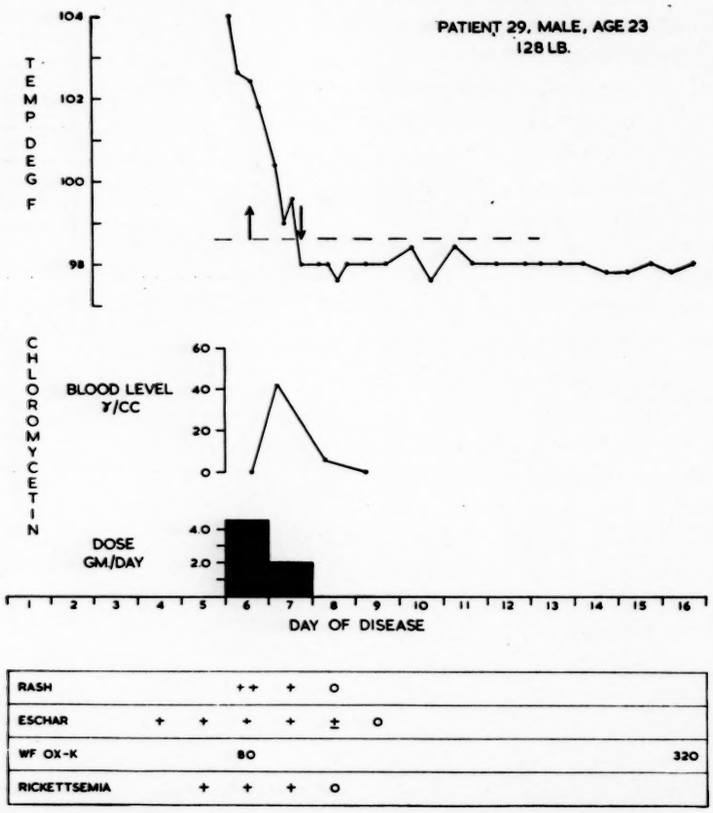


FIG. 2. Clinical response of patient with scrub typhus to chloramphenicol therapy begun on the sixth day of disease. A total of 6.5 Gm. of chloramphenicol was given over a period of twenty-two hours. (Reproduced from *J. Clin. Investigation*, 28: 1196, 1949.[24b])

Spotted Fever. Pincoffs and his co-workers[30] obtained excellent results with chloramphenicol in the treatment of fifteen patients suffering from Rocky Mountain spotted fever. These persons, who were carefully studied during the spring and summer of 1948, were given an initial oral loading dose of 75 mg. per Kg. of body weight followed by 0.5 Gm. every three hours until the temperature had been normal for a twenty-four-hour period. The average duration of fever after initiation of therapy was approximately 2.2 days. The duration of the febrile response in each of

the fifteen cases is presented graphically in Figure 3. A number of the patients were desperately ill but all recovered.

For comparison the Baltimore group analyzed the records of forty-six patients with spotted fever who were treated at the University Hospital between 1930 and 1946 and who recovered without benefit of specific therapy and without complications. The average duration of fever in these cases was 16.0 days. The authors point out that in Maryland during the past decade the mortality from Rocky Mountain spotted fever has been about 20 per cent.

General Remarks. In general, a therapeutic schedule which seems applicable to adult patients suffering from the rickettsial diseases is as follows: An initial loading dose of 3.0 to 4.0 Gm. of chloramphenicol given by mouth, followed by 0.25 Gm. doses every two or three hours until the temperature returns to a normal level. Such a schedule usually requires 5.0 to 10.0 Gm. of drug over a period of one to three days.

Reports have not yet appeared on the use of chloramphenicol in patients with Q fever or rickettsialpox, both of which diseases occur in the United States. Laboratory data on experimental infections caused by the agents of these rickettsial diseases would lead to the belief that the drug should be useful in the treatment of such patients.

Bacterial Diseases

Typhoid Fever. Two patients originally presumed to have scrub typhus and treated with chloramphenicol by the American group in Malaya subsequently were proved to have typhoid fever; these patients became afebrile in three to four days. As a result studies on this disease were pursued intensively. The data obtained from the first ten cases of typhoid fever who received chloramphenicol clearly indicated that the antibiotic had a specific therapeutic effect in this bacterial disease. The average duration of fever in this group of patients after treatment was instituted was 3.5 days.[17a] The graphic record of one of the first patients is presented in Figure 4.

The extensive experience of the Army group, gained in the treatment of forty-four patients with typhoid fever, confirmed the early observations.[17,23] These investigators pointed out that the patients became afebrile before the intestinal lesions of typhoid fever healed and as a result hemorrhage and perforation sometimes occurred during or shortly after defervescence. In their summary of the first twenty-four patients treated they reported intestinal hemorrhage in two persons and intestinal perforation in another. Nevertheless, all of these treated patients recovered.[17b]

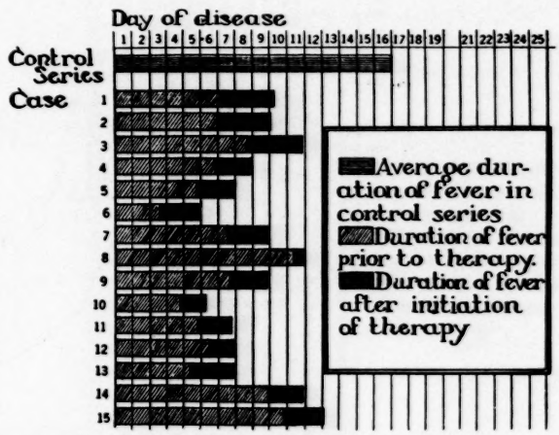


FIG. 3. Duration of fever in fifteen cases of Rocky Mountain spotted fever treated with chloramphenicol contrasted with average duration of fever in control series of forty-six cases. (Reproduced from *Ann. Int. Med.*, 29: 656–663, 1948.[30])

The Army group encountered relapses of typhoid fever in two of the first ten treated patients. Subsequent studies demonstrated that the incidence of relapses was related to the duration of chloramphenicol therapy.[23] Thus a clinical relapse with reappearance of bacteremia occurred in seven of the thirteen patients whose initial course of drug was given for eight days or less; the average duration of therapy was 6.9 days. No relapses occurred in another group of nineteen patients which was comparable in essentially all respects except that the treatment was continued for nine to fourteen days, average 11.2. Similarly, no relapses were encountered in a third group of twelve patients whose therapy was continued for

fourteen to twenty-three days. On the basis of these findings it would appear that patients with typhoid fever should receive 25 to 30 Gm. of chloramphenicol over a period of ten to twelve days. This can be given in the following manner: After an oral loading dose of 3.0 Gm. the patient may be given a total of 3.0 Gm. daily in divided doses until the fever disappears. Subsequently the patient should receive 2.0 Gm. daily for the next eight to ten days.

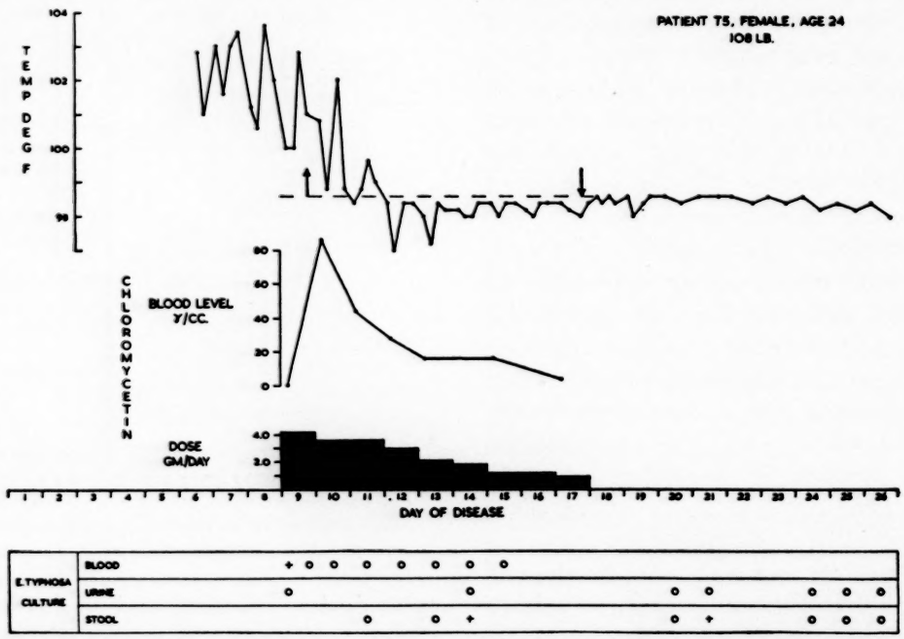


FIG. 4. Clinical response of typhoid patient to chloramphenicol therapy. A total of 22 Gm. was given over a period of nine days. (Reproduced from *Ann. Int. Med.*, 29: 131–134, 1948.[17a])

In general, S. typhosa were no longer demonstrable in the bloods of the patients a few hours after chloramphenicol therapy was begun. Furthermore, the blood remained sterile thereafter except in those instances in which relapses occurred. About one-half of the patients had S. typhosa in their stools on one or more occasions after chloramphenicol therapy was begun. Stools from the majority of these did not yield the organisms after therapy was discontinued; indeed, the reappearance of S. typhosa in the stool was limited almost entirely to those individuals who suffered relapses. The incidence of the typhoid carrier state did not appear to be higher in the treated group than it was in the large groups of patients who recovered before the advent of specific therapy.[17b] Chloramphenicol appears to be of no value in eradicating the carrier state of typhoid fever.[17b,31]

Confirmatory evidence regarding the value of chloramphenicol in the treatment of typhoid fever has accumulated rapidly. McDermott and his associates during the course of therapeutic trials in Mexico in the fall of 1948 reported experiences similar to those of the Army group in Malaya.[32] More recently the drug has been shown to be of value in the treatment of a number of patients with this disease in the United Kingdom[33,34] and the United States.[35]

Brucellosis. Woodward and his associates[36] reported on the results of administering chloramphenicol to nine patients with brucellosis. Six of these were experiencing an initial attack and three were suffering a relapse which had begun two to five months after the primary illness had been controlled by combined streptomycin and sulfadiazine therapy. In four of the patients Brucella

abortus was cultured from the blood, in two B. suis and in one B. melitensis. The diagnosis in the two remaining cases was established by agglutination tests. The clinical record of one of these patients is reproduced graphically in Figure 5. The

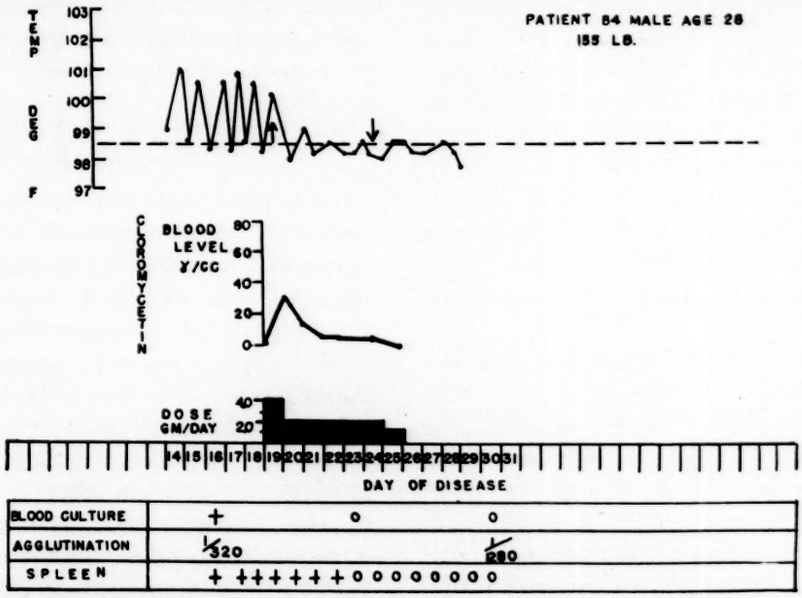


FIG. 5. Clinical response of patient with brucellosis (B. suis) treated with 15.5 Gm. of chloramphenicol over a period of seven days. (Reproduced from *J. Clin. Investigation*, 28: 968, 1949.[36])

average duration of fever after therapy was begun was 2.7 days for the nine patients.

The therapeutic regimen employed in this group of patients was similar to that used in typhoid fever. Following the initial loading dose of approximately 50 mg. of chloramphenicol per Kg. of body weight, the patients were given 0.25 Gm. doses at three-hour intervals until the temperature became normal and for a minimum of five days thereafter. The majority of patients were followed for six to nine months after treatment. One individual suffered a relapse thirty days after chloramphenicol was discontinued. This febrile episode was promptly terminated when therapy was again instituted.

The authors concluded that chloramphenicol was superior to the earlier forms of treatment. They also concluded that at this time it was impossible to decide which of the two new antibiotics, i. e., chloramphenicol and aureomycin, was the drug of choice for this disease.

Harris' experience, although more extensive than that of Woodward, provided less definitive information. Among the 110 patients with brucellosis who were treated with aureomycin and twenty-five who received chloramphenicol, the diagnosis was proved culturally in only one instance.[37]

Gonorrhea. During the work of the Army research team in Malaya one of the volunteers in a scrub typhus chemoprophylactic test developed acute gonorrheal urethritis shortly before he was due to receive his first oral dose of 3.0 Gm. of chloramphenicol. Treatment of the urethritis was delayed in order to see what effect the scheduled dose of chloramphenicol would have on the gonorrheal infection. The discharge in this individual cleared within twenty-four hours after the drug was given. Subsequently a total of forty-eight Malayan males with acute gonorrheal urethritis were treated with a single oral dose of 1.0 to 1.5 or 3.0 to 3.5 Gm. of either fermentation or synthetic chloramphenicol.[18] The clinical response was essentially the same in each subgroup. Dysuria disappeared within thirty-six hours

(average for the forty-eight patients) and discharge (as determined by the absence of exudate on stripping) within forty-nine hours. Smears of the discharge with few exceptions were free of gonococci by the next day and leukocytes generally were absent from the discharge in those instances in which this sign persisted longer than forty-eight hours. Ten patients, or approximately 20 per cent of this entire series, had relapses during the month following treatment. There was no apparent difference in the number of recurrences in the various subgroups. All patients with relapses were treated with a single oral 3.0 Gm. dose of chloramphenicol and all responded satisfactorily.

The authors were of the opinion that the therapeutic results in this infection compared favorably with those obtained by other methods of therapy. They pointed out that chloramphenicol appeared to have limited effect in experimental syphilis in rabbits and that their results in two patients with syphilitic chancres were essentially comparable to those reported in infected rabbits. Therefore, it seemed possible that doses of chloramphenicol which were adequate to cure the Neisserian infection might not suppress a syphilitic infection which was in the incubation period.

Other Bacterial Infections. There are a number of reasons why chloramphenicol should be of value in the treatment of urinary tract infections. In the first place, larger amounts of antibiotic are found in the urine than in the blood. Secondly, many of the bacteria commonly found in urinary tract infections are readily inhibited by the antibiotic. Chittenden and his co-workers[38] found that the urine of infected patients became free of bacteria within a day or so after chloramphenicol treatment was instituted in the form of 1.0 to 3.0 Gm. daily. These workers emphasized that complicating factors which interfere with urinary flow must be corrected if the infection is to be permanently controlled.

The causal organisms of a number of bacterial diseases of man are susceptible to chloramphenicol. Although reports of the use of this new antibiotic in the treatment of patients with these diseases have not yet appeared in the literature, they will be awaited with interest. Some of these infections are whooping cough, influenzal meningitis, Friedländer's pneumonia, plague, bacillary dysentery, cholera, melioidosis and perhaps even tuberculosis.

CHLORAMPHENICOL IN OTHER INFECTIOUS DISEASES OF MAN

One published report has appeared on the use of chloramphenicol in a patient with atypical pneumonia associated with the development of cold agglutinins.[39] The results of future experience in the therapy of this disease must be awaited before any conclusions are warranted. It will be recalled that atypical pneumonia is a clinical syndrome having a variety of etiologic agents but that the causal agent of the disease associated with the cold agglutination phenomenon has not been transmitted to animals.[40] Chloramphenicol is effective against R. burneti and the virus of psittacosis, both of which may produce pulmonary disease indistinguishable from primary atypical pneumonia of unknown etiology. Therefore, in future studies it will be important to employ all of the available diagnostic procedures in order to establish the etiology of each case of treated atypical pneumonia.

The experimental infections with the virus of lymphogranuloma venereum, which is closely related to the agent of psittacosis, are readily controlled by chloramphenicol. It is to be expected that the drug will prove of value in treating human disease caused by this virus.

Another of the venereal diseases, i. e., granuloma inguinale, appears to respond to chloramphenicol. Greenblatt and his associates[41] reported good results in five patients with this infection who received 20 Gm. of drug over a period of five to ten days. Donovan bodies were no longer demonstrable in the lesions a few days after therapy was begun.

Chloramphenicol has some *in vivo* effect on several members of the family Treponemataceae. Whether it will be of value in the treatment of patients with relapsing fever or with syphilis remains to be seen. The Army group in Malaya[18] observed two patients with primary syphilis in whom the spirochetes disappeared and the primary lesion healed after several days of oral therapy. However, both of these individuals developed recurrent lesions at the sites of the original chancres about a month later. In view of the efficacy of established methods of antiluetic treatment, studies on chloramphenicol therapy in syphilis should be restricted to a few specialized centers until adequate evaluation is obtained.

TOXICITY OF CHLORAMPHENICOL FOR MAN

The presence of the nitrobenzene radical in the structure of chloramphenicol led to the suspicion that the drug might be toxic for the hemopoietic system. Careful observations on a relatively large number of patients with scrub typhus or with typhoid fever who were treated with the antibiotic have failed to show any significant change in the red blood cells or white blood cells attributable to therapy. Furthermore, none of these cases has shown evidence of renal or hepatic involvement.[17,24]

Occasional individuals who receive large single doses have transient mild euphoria. A number of persons complain of mild gastrointestinal disturbances characterized by moderate gaseous distention and a slight change in the consistency of the feces for a few days. A few persons, limited almost entirely to the group receiving drug for a period of a week or more, develop glossitis. This is characterized by tenderness, hyperemia and marked prominence of lingual papillae. Glossitis continues during the period of therapy and for a few days after the drug has been stopped. After prolonged administration of the antibiotic pruritus ani has been noted in a few instances.[42]

No serious toxic manifestations have occurred as a result of chloramphenicol therapy. In fact, the untoward reactions so far observed have been minor in character. It must be realized, however, that the drug is only now coming into wide usage and careful search for such manifestations should be continued.

CONCLUSIONS

Chloramphenicol is a highly effective therapeutic agent against a number of infectious diseases of man. Among these the rickettsial diseases, typhoid fever, brucellosis and gonorrhea are presently in the foreground.

The drug has potential usefulness against other diseases caused by a wide variety of etiologic agents.

It is worth while to compare the experimental data summarized in this article with those dealing with aureomycin.[43] Both antibiotics are amazingly similar in their therapeutic effectiveness in a wide range of infections. Despite these similarities the two are not identical. The chemical structure of chloramphenicol is simple and the drug has been synthesized on a commercial scale; neither of these points applies to aureomycin. Chloramphenicol is a specific for typhoid fever while aureomycin is not. Neither drug appears to be dangerously toxic but annoying reactions are more frequent following aureomycin than chloramphenicol. The medical world is fortunate in having acquired within the past two years two such valuable antibiotics as chloramphenicol and aureomycin. It is safe to assume that the limits of application of both of these have not yet been reached.

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Case Reports

Tetanus Following Dental Extraction*

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TETANUS is a rare disease in northeastern United States. In 1937 Huntington, Thompson and Gordon[1] collected only 642 cases from the records of eighteen hospitals situated in this area. During the peacetime period of 1920 to 1929 the United States Army with an average strength of 130,000 men reported eight cases.[2] Between 1939 and 1943 there were 3,105 deaths from tetanus in the United States.[3] The average annual mortality was 621. At this hospital there have been only five cases in 219,408 admissions during the past twenty-five years. Of the four previous cases two occurred in 1923, one in 1925 and one in 1943. There was one death.

The low incidence of tetanus contributes to the difficulty in diagnosis. Vinnard[4] reported that in his series of 352 patients treated at the Charity Hospital in New Orleans between 1934 and 1944 twenty-six cases were not diagnosed at first. Of this series fourteen were admitted to the hospital for one to seven days before the correct diagnosis was made.

Following the development of clinical signs of tetanus the prognosis depends on early diagnosis and treatment.[5–7] Since the mortality is estimated at between 20 and 50 per cent,[4,5] the importance of early diagnosis is self-evident.

CASE REPORT

This was the third hospital admission of J. S., a sixty year old colored male complaining of inability to open his mouth, pain in his jaw, back, hips and knees. The past history revealed that he had a primary luetic infection at the age of twenty-six. For the three years previous to admission he had been treated with bismuth and arsenicals at another institution. Spinal serology was negative in 1932. The patient's first admission was in 1936 with the diagnosis of syphilitic aortitis and mild cardiac decompensation. His second admission occurred in 1937 with the diagnosis of syphilitic aortitis, alveolar abscesses, treatment for an error in refraction and extraction of two teeth. Spinal serology was negative. Since 1937 he had been followed in the cardiac clinic with minimal symptoms and physical findings. In September, 1946, he appeared at the dermatology clinic with a hemostatic ulcer of his left lower leg secondary to varicose veins. By August 1, 1947, it had been considered healed but he was still being treated with 1 per cent ichthyol and Lassar's paste at the time of admission.

Thirteen days before admission the patient had the upper left second molar extracted using novocain anesthesia. Six days before admission he reported not feeling well and complained of a head cold. Four days before admission and nine days following the extraction the patient appeared at the out-patient department complaining he could not talk. His jaw could be opened 1 cm. No tenderness was found on examination. There was no Chvostek sign. Deep reflexes were normal. It was noted that the masseter muscles seemed to go into spasm on attempted opening of the jaw. The patient was seen again that afternoon when it was observed that his jaw appeared swollen about the temperomandibular joint. It was thought that he had a subperiosteal abscess. Surgical consultation was obtained. His temperature was 99.6° orally. There was no local tenderness nor any cervical lymphadenopathy.

Three days before admission and ten days following the dental extraction he returned to the out-patient department where no oral lesion was found to warrant trismus. There were several abrasions of the tongue. Although his

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bite was very powerful, his jaw could be opened wide with a tongue depressor. His condition was considered emotional. Two days before admission he was seen again at the out-patient department. Trismus was still present and poor coordination of his legs was noted. During the three days prior to admission he experienced progressive stiffness of his back and legs, with a developing opisthotonos, constipation and inability to void.

He was admitted by ambulance in severe trismus and extreme opisthotonos. There was no history of convulsions. A tongue depressor could not be forced between his teeth. He experienced difficulty in respiration and breathing was stertorous. There was no history of any cut, puncture wound, splinter or other such portal of entry, nor did physical examination reveal any such evidence. He was admitted with the diagnosis of tetanus. On physical examination the patient was seen to be a fifty year old colored male in acute distress and in severe opisthotonos. Temperature was 99.4°, pulse 80 and respiration 20. He was able to speak only with difficulty and bloody mucus ran from between his teeth. Periodic generalized tonic convulsions, lasting ten to fifteen seconds, began shortly after his admission to the ward. Risus sardonicus was present. Trismus prevented insertion of a tongue depressor blade to open the jaw forcibly more than a ½ cm. By retracting his cheek and inspecting the tongue from the side where his teeth were missing the tongue appeared bloody and lacerated. The site of the dental extraction was poorly visualized because of the trismus and bloody mucus. Forcing the jaw open caused masseter spasm. His neck was rigid and hyperextended. There was no cervical lymphadenopathy. His heart rate was slow and regular. There were no murmurs or enlargement of the heart. On examination of his abdomen there was generalized resistance, and some tenderness was present in the lower aspect of the right rectus muscle. There was stiffness and rigidity of the lower extremities. On passive motion the knee and hip joints could be moved forcibly but incompletely. On the anteromedial aspect of the lower third of the left leg there was a shallow ulcer ½ cm. in diameter with a granulating base. Deep reflexes were 2+ and bilaterally equal and active. Babinski reflexes were negative.

Laboratory data were as follows: Urine analysis revealed a specific gravity of 1.009; albumin, negative; sugar and microscopic examination, negative. Hemoglobin was 14.9 Gm., 100 per cent, with 9,000 white blood cells, polymorphonuclear cells, 78 per cent, and lymphocytes, 22 per cent. The white blood count rose to 12,900 on his sixth hospital day but then returned to normal. Mazzini and Kolmer tests were 4+ positive. Urea nitrogen was 8.4 mg. per cent; sugar, 96 mg. per cent; calcium, 10 mg. per cent; phosphorus, 3.7 mg. per cent; alkaline phosphatase, 1.3 Bodansky units per cent; total proteins 6.8 Gm. per cent, with the albumin 3.9 Gm. per cent and globulin 2.9 Gm. per cent. The sedimentation rate was 28 mm. on admission, rose to 65 mm. by the nineteenth day and returned to normal at the time of his discharge. Cultures from the dental extraction site and leg ulcer were negative for tetanus bacilli. Spinal fluid was clear; it showed 5 cells per cc., 3 being red blood cells and 2 white blood cells. Spinal fluid protein was 70 mg. per cent. There was no serology report. Guinea pig test for tetanus using the spinal fluid was negative. A chest plate showed slight left ventricular hypertrophy of the heart and a moderately tortuous but not dilated aorta. Electrocardiogram showed normal rhythm, left axis deviation and ventricular ectopic extrasystoles.

A lumbar tap was attempted the night of admission but it was unsuccessful because of extreme opisthotonos. A large pillow was placed under his arched back for support.

He was immediately given tetanus antitoxin 40,000 units intravenously, soluble phenobarbital 4 gr., morphine sulfate ⅙ gr. and penicillin 30,000 units intramuscularly. Following this he received tetanus antitoxin 40,000 units intravenously every six hours, with soluble phenobarbital 2 gr. every six hours and penicillin 100,000 units intramuscularly every three hours. During this time he was given sedatives to control his spasms but not so deeply as to give him respiratory depression.

On the morning following admission it was noted he was worse. He was unable to talk because of the trismus and sore tongue. A neurosurgical consultation was obtained and a lumbar tap was performed by a lateral approach to the spinal canal. Normal manometrics and clear fluid were found. Tetanus antitoxin 20,000 units were instilled, the only time this route of administration was used. The patient was maintained on parenteral fluids daily: 1,500 cc. 5 per

cent glucose in normal saline, amigen 1,000 cc. and vitamins.

During his first hospital day he experienced several generalized tonic spasms lasting thirty to forty-five seconds and characterized by twitching of the facial and cervical muscles, tightening of the lips, blowing of blood-tinged foam from the mouth and general rigidity. Suction was used at this time since his mouth could be opened about 1 cm.

Neurologic consultation confirmed the diagnosis of tetanus. On surgical consultation it was noted one could get tetanus from a superficial crusted area, but that this patient's leg ulcer was not crusted and thus seemed an unlikely portal of entry. On dental consultation it was noted that the socket appeared to be healing satisfactorily.

By the night of his first day he had received 120,000 units of antitoxin intravenously and 20,000 intrathecally. On the morning of his second day, while trying to void, he experienced tonic contraction of the muscles with increased opisthotonos and generalized rigidity lasting forty-five seconds. He was catheterized and 700 cc. of urine were obtained. By his second day he had shown some improvement. He could open his mouth 1 inch and there was a reduced amount of temperomasseter spasm following forced opening of the mouth. He had a fever of 101°F. during this time. His leg ulcer had healed so that no more than the admission culture was obtained.

By the third day two fingers could be inserted into his mouth. He could talk better and could flex his head slightly on passive motion. The opisthotonos had cleared. At the end of the third day he had received 440,000 units of antitoxin intravenously. By the end of the fourth day this amounted to 520,000 units when the dosage by this route was stopped and he was given 5,000 units intramuscularly daily for only the following three days. By the sixth day he was taking a high calorie fluid diet, he could be gatched up in bed and he could turn himself in bed without assistance. His tongue was treated with gentian violet. On the seventh day he could place his chin within two fingers of his sternum. His main complaint was of a sore tongue.

On his tenth and thirteenth days he received 1,500 units of antitoxin intramuscularly which ended the course of treatment with the antitoxin. With reduction in sedation the patient became more alert on his tenth hospital day. By the eleventh day his chin could be moved to the sternum and he could feed himself. By the thirteenth day he complained only of weakness and also of continued soreness of his tongue. There was no remaining spasticity of his muscles. Reflexes were physiologic and equal but coordination of the fingers was poor. He was started on physiotherapy. By the fourteenth day he was allowed up progressively. At this time penicillin was stopped. From this point on he showed both subjective and objective improvement. His sedimentation rate reached its maximum level of 65 mm. on the nineteenth day but dropped to 25 mm. at the time of discharge.

His total tetanus antitoxin dosage had been 520,000 units intravenously, 23,000 units intramuscularly and 20,000 intrathecally, an over-all total of 563,000 units. He experienced no serum sickness.

Finally on the thirtieth hospital day he was discharged to the convalescent home.

COMMENTS

Three of Vinnard's fourteen patients admitted to the Charity Hospital were initially diagnosed as cases of hysteria, as was our patient in the clinic. But in hysteria self-traumatization is rarely carried to the point of painful laceration of the tongue.

The history, physical findings and course of our patient leave no doubt as to the diagnosis despite negative cultures. Culturing of the tetanus bacillus is often unsuccessful[8,9] and negative results do not eliminate the diagnosis; neither does a negative guinea pig test rule out the diagnosis.

The portal of entry presented a peculiar problem. The patient had experienced none of the classical traumas associated with portals of entry. He had had a leg ulcer secondary to varicose veins for thirteen months, but this had been improving under treatment and on admission it appeared as a small, shallow, granulating ulcer which after bed rest and administration of penicillin healed within forty-eight hours. We are left with the history of a dental extraction nine days before the onset of trismus. In our opinion this time relationship is more than a mere coincidence since the incubation period of six to twelve days is the most frequently encountered in tetanus.[8,10]

Although tetanus following dental extractions is relatively rare, it has been reported. Graves[10] in his report on 813 cases found three following dental extraction. Appleton[11] in 1933 found only three other cases reported in the literature.

In this case the portal of entry was the tooth socket. It is interesting on two accounts: First, because such a portal is relatively rare; second, because the fact that there had been an extraction so clouded the clinical picture that the correct diagnosis was delayed.

Treatment was carried out conservatively as outlined in recent papers.[4–6,12] Tetanus antitoxin was given intravenously every six hours so that by the fourth day he had received 520,000 units. Restlessness and tonic convulsions were adequately controlled by phenobarbital given parenterally. Penicillin was given to ward off secondary infection, particularly hypostatic and aspiration pneumonia, not as therapy specific for the tetanus bacillus. There is controversy as to its specificity, most of the evidence pointing toward its being significant only against secondary infection.[3,13–15] Supportive measures were also considered important. Parenteral fluids and vitamins were given. He was turned frequently. Constipation and urinary retention were treated.

The patient's respiratory distress was controlled by sedation which never reached the point of danger so that the use of curare was not thought to be warranted.[16–19] In a careful study of the use of curare in tetanus Adriani and Ochsner[17] concluded that the dosage needed to initiate significant muscular relaxation was not adequate until complete curarization was attained. They found that respiratory depression and obstruction were difficult to avoid.

SUMMARY

A case of tetanus is presented. Evidence is given to support the thesis that the site of a dental extraction was the portal of entry.

Treatment is briefly discussed.

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Loeffler's Syndrome with Associated Eosinophilic Polyserositis*

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CASE reports of the syndrome first described by Loeffler in 1932 have been numerous in European but relatively infrequently encountered in the British and American literature. The current concept of the pathogenesis of the syndrome ascribes it to hypersensitivity and suggests that involvement of any tissue may be a feature. Because of the apparent rarity of associated pericarditis with effusion, this case was considered of unusual interest.

CASE REPORT

Mrs. D. S., a thirty-seven year old white married housewife, was admitted to the Wisconsin General Hospital on April 18, 1947, complaining of persistent low grade fever. Her illness had begun during a "flu" epidemic four weeks prior to admission and consisted of fatigue, weakness and anorexia. However, she failed to recover as did the rest of the family and became progressively more dyspneic and orthopneic. She had drenching night sweats and a cough productive of about one-fourth cup of thick white sputum a day. Following a chest roentgenogram on April 7, 1947, she was hospitalized by her local physician and given a course of 1,500,000 units of penicillin. Antihistaminic drugs were also used. In spite of this she did not improve.

Laboratory studies at that time were significant in that with a total count of 11,800 leukocytes there were 30 per cent neutrophiles, 28 per cent lymphocytes and 42 per cent eosinophiles. The sputum showed no acid-fast bacilli. The Mantoux test was negative. The roentgenogram taken on April 15, 1947, showed progression of the infiltration in the lungs and she was referred to the Wisconsin General Hospital for further study.

The past medical history included two episodes of fever, cough and other symptoms suggestive of pneumonia. The first occurred at the age of nineteen, shortly after the onset of symptoms diagnosed as "asthma" and necessitated two months of bed rest. The second, at the age of twenty-nine, was more severe and was associated with fever, pleurisy and night sweats. After a chest roentgenogram she was told she had "galloping consumption." However, her sputum was reported to be negative for tubercle bacilli and after three months she recovered completely. She also gave a history of chronic sinusitis, giant urticaria at times and frequent attacks of asthma, some so severe that she required oxygen therapy. She had had nasal polyps removed six or seven times. There was no known contact with tuberculosis.

The family history contributed the fact that her mother had died of Hodgkin's disease (proved by biopsy) and that her two children had asthma and hay fever.

On physical examination she was small, slender, well developed, appeared younger than her stated age and looked chronically ill. The temperature was 99°F., pulse 100 and blood pressure 100/76. Pertinent physical findings were limited to the chest where increased fremitus and breath sounds, and a few posttussive rales in the right upper chest were noted.

Blood examination showed 12.9 Gm. of hemoglobin with 5,200,000 red cells, 11,400 leukocytes, 37 per cent of which were neutrophiles, 16 per cent lymphocytes, 4 per cent monocytes, 40 per cent eosinophiles and 3 per cent metamyelocytes. Another leukocyte count showed a total of 11,950 with 45 per cent eosinophiles.

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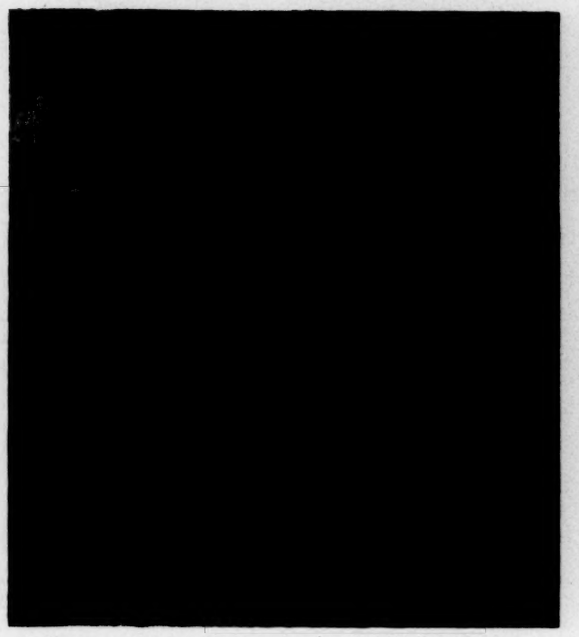


FIG. 1. Chest roentgenogram April 19, 1947.

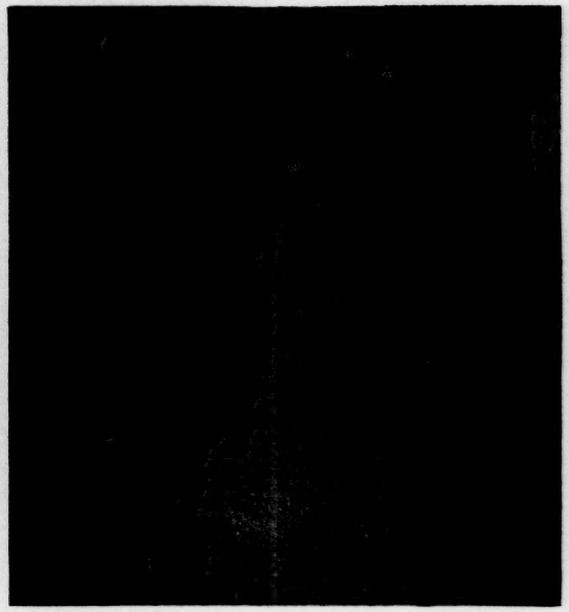


FIG. 2. Chest roentgenogram June 3, 1947.

Her sputum showed no tubercle bacilli or fungi on smear and culture. A skin test was negative with 1 mg. of old tuberculin. Her chest roentgenogram showed the heart size to be normal. (Fig. 1.) There was a distinct thickening of the hilum shadows bilaterally with a nodular appearance on the left. There was coarse, stringy, infiltrative density radiating out from the left hilum into the lung field in the central portion and well marked pleural thickening over the upper lobe. On the right side there was a generalized patchy and conglomerate density scattered throughout the lung field. When compared with previous roentgenograms it was evident that there had been some apical thickening and fibrosis in 1943. The pneumonic process demonstrated in the 1947 films was present chiefly on the right side and underwent considerable fluctuation with regression and recurrence until the last roentgenogram dated April 15, 1947. Since that time there had been clearing of the consolidation but a spread to the right base had occurred.

When studied by the Allergy Department there were no reactions to scratch tests but on intradermal tests there were immediate reactions to grass pollen, feathers, wool, orris root, milk and chocolate, and delayed reactions to tree pollens, ragweed pollen, molds, rabbit hair, house dust, pork and egg. Bacterial vaccines showed large reactions.

It was believed at this time that the patient had Loeffler's pneumonia and she was discharged on April 24, 1947, with the recommendation that contact with the forementioned substances be avoided and desensitization to house dust, bacterial vaccine and co-seasonal pollen be attempted.

The patient was readmitted on May 22, 1947, complaining of pain in the neck, a change in voice and difficulty in swallowing which had developed abruptly one week before. The following day she developed soreness over the precordium and an aching pain in the left arm. Usually the pain was increased on motion and change of position. The pain radiated to her back and at times was so severe that she could be comfortable only when sitting up and leaning forward. She had been conscious of a more rapid heart rate.

The physical examination revealed an anxious but not acutely ill white female who preferred to lie on her left side. The temperature was normal, pulse rate 134 and blood pressure 90/70. The area of cardiac dullness was increased, the heart tones were distant and a pericardial friction rub was heard. There were scattered musical rales throughout the chest. There was epigastric tenderness but the liver edge was not palpated. No paradoxical pulse could be demonstrated.

Again the eosinophiles varied from 20 to 47 per cent in a total of 7,650 to 11,500 leukocytes.

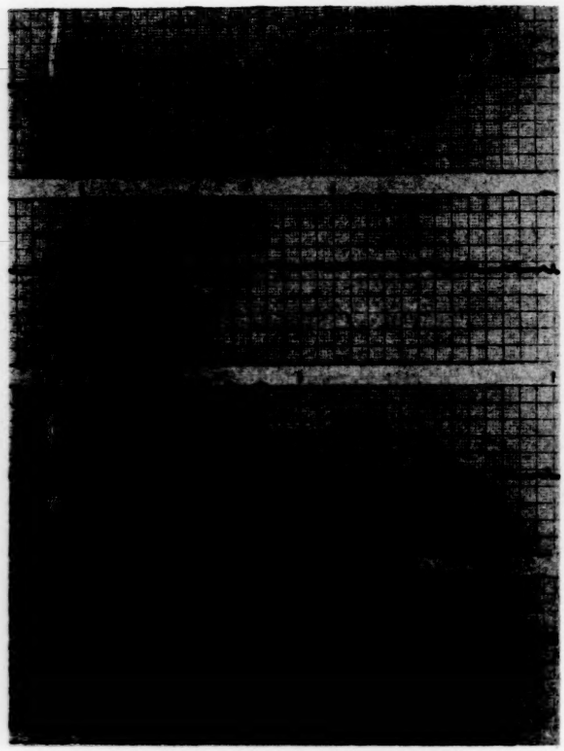


FIG. 3. Electrocardiogram.

The chest roentgenographic and fluoroscopic examinations confirmed the clinical impression of pericardial effusion. (Fig. 2.) The electrocardiogram was of the pattern noted in pericarditis. (Fig. 3.)

Two diagnostic pericardial aspirations were done and 150 cc. of slightly blood-tinged fluid was removed on each occasion. Of the 3,000 leukocytes per cu. mm. of this fluid, 69 per cent were eosinophiles. The erythrocyte count in the fluid was 71,000 per cu. mm. Cultures of this fluid were negative on aerobic and anaerobic media as well as for tubercle bacilli. Agglutinations for B. abortus, B. tularense and B. typhosus on this fluid were likewise negative.

A sputum smear showed numerous eosinophiles. A skin test with coccidioidin was negative. The chest roentgenogram showed the cardiac enlargement consistent with pericardial effusion and a small left pleural effusion. At this time the pulmonary parenchyma was essentially normal on the right and considerably less involved on the left than previously.

On the fifteenth hospital day the patient had a sudden sharp pain in the left calf. This was of relatively short duration and she did not report it until the following day. At that time there was

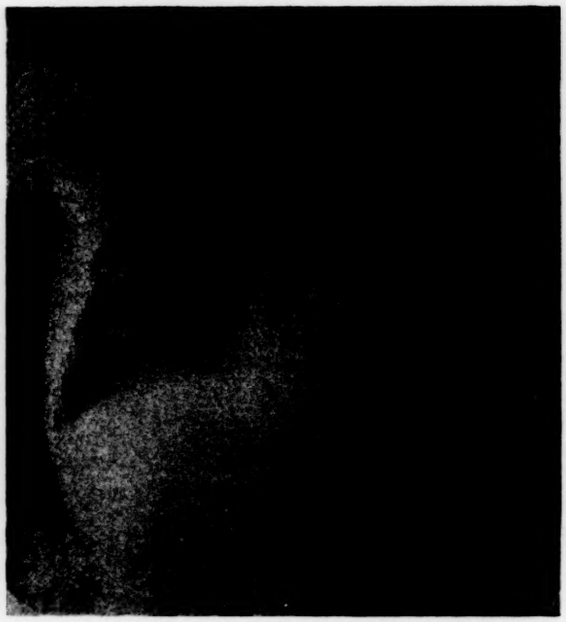


FIG. 4. Chest roentgenogram October 6, 1947.

evidence of venous thrombosis with swelling, discoloration and tenderness on pressure over the calf and the inner aspect of the left thigh. She was treated with heparin and then Dicumarol and the symptoms subsided promptly. On discharge from the hospital June 22, 1948, the pericardial friction rub had been absent for several days and the chest roentgenogram showed only slight cardiac enlargement. The pulmonary parenchymal densities had cleared almost completely.

On July 10, 1947, she was seen as an outpatient. Her symptoms were again suggestive of recurrent pericarditis. There was no recognized pericardial rub, but fluoroscopic examination showed increase in the size of the cardiac silhouette consistent with a small pericardial effusion. In the right upper lung field there were scattered densities. The leukocyte count was 12,050 with 20 per cent eosinophiles.

In October, 1947, the patient was seen by Dr. A. M. Olsen of the Mayo Clinic. He wrote that sputum cultures were again negative for tubercle bacilli as well as for pathogenic fungi. Tuberculin, coccidiodin and histoplasmin skin tests were all negative. The chest roentgenogram at that time revealed bilateral upper lung field densities. The cardiac silhouette was larger than on the chest roentgenograms of April, 1947, but was not diagnostic of pericardial effusion. (Fig. 4.) The left vocal cord was paralyzed.

Failure to obtain any symptomatic relief from the treatment outlined prompted this patient to go to Arizona. A recent report from the patient's referring physician stated that she had not improved and was bedridden.

COMMENT

This patient had three illnesses which were in all probability recurrent episodes of Loeffler's pneumonia. During the first two experiences complete resolution occurred and no residual pulmonary damage was evident clinically or by roentgen study. In the third episode, the onset was similar and for a period of time the changes were limited to the lungs. The changes were reversible at this time as evidenced by the complete clearing and then recurrence of the parenchymal infiltrates. The serous membrane involvement was evident in the pericardium and pleura. The pericardial effusion subsided. However, because of the subsequent course characterized by continued difficulty in breathing without asthmatic episodes, it is suggested that constrictive pericarditis had developed. Unfortunately, we have not had the opportunity of repeating the examination. The appearance of thrombophlebitis without recognized cause leads to the impression that it was due to vascular damage from the same allergic stimulus. A muscle biopsy was not obtained so that morphologic changes in blood vessels could not be demonstrated.

This patient's course is very similar to that of several others reported by Harkovy. His report deals with sixteen cases, fifteen of which were suffering from typical bronchial asthma. The attacks of asthma were accompanied by pulmonary lesions and reactions of serous membranes, including pleura, pericardium and peritoneum. The fluids from these serous cavities were sterile and the eosinophile content was very high. The peripheral blood showed eosinophilia in all cases. Four of the sixteen that came to autopsy were characterized by thickening of the intima of small vessels, necrotizing arteritis, endoarteritis obliterans and fibrosing arteritis in the lungs, serous membranes, myocardium and other organs. The variety of clinical syndromes presented is explained by the number of "shock" tissues that may be involved, either by a reversible or irreversible process. The allergic nature of this patient's illness is suggested by the long history of bronchial asthma, nasal polyposis, urticaria and the allergic state of her two children. The eosinophilia in the peripheral blood and the pericardial fluid is further evidence of the allergic nature of her disease.

CONCLUSION

A case of pneumonia associated with pericardial effusion and venous thrombosis is reported. That the various features of this patient's illness were due to hypersensitivity is supported by the history of bronchial asthma and the discovery of eosinophilia in the blood, sputum and pericardial fluid.

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Kala-azar*

With Special Studies of Bone Marrow and Lymph Nodes

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KALA-AZAR (visceral leishmaniasis) is a tropical disease that was rarely seen in this country before World War II, only eight cases having been reported in the United States.[1–8] It has been estimated by Most[9] that fifty to seventy-five cases occurred in American personnel during the recent war. Many more cases may manifest themselves during the next few years. The disease should be of interest to physicians who care for veterans, particularly as there is available specific therapy which dramatically alters the high mortality rate of untreated patients.

This report presents an instance of kala-azar in a veteran of the North African, Sicilian and Italian campaigns. He had been treated as a case of malaria for over two years before the proper diagnosis was established. A detailed study of bone marrow biopsy is included to demonstrate the high incidence of parasitized cells in the reticuloendothelial system and to emphasize the diagnostic value of this procedure.

CASE REPORT

W. A. N., a twenty-eight year old white male, a World War II veteran, was admitted to the Lawson Veterans Administration Hospital on October 27, 1947, complaining of fever, weakness, distention of the abdomen and weight loss of 25 pounds. In July, 1944, while in Southern Italy, he developed generalized aching, chills, fever and headaches. He was admitted to an Army hospital where malarial parasites were said to have been found on blood smear and quinine therapy was instituted. His symptoms improved and after eight days he was discharged. Two weeks later he returned to the hospital with similar complaints. Although repeated examinations for malarial parasites were negative, he was given antimalarial therapy and improved again, but he continued to run a low grade fever after returning to duty. In July, 1945, there was a mild reappearance of symptoms that did not require treatment or hospitalization. He was returned to the United States in August of that year and was separated from the service. Episodes of malaise, generalized aching, chills and fever occurred in November, 1945, November, 1946, March, 1947 and June, 1947. On two occasions he received further antimalarial therapy although malarial parasites were not demonstrated. During the two years before admission he had noted progressive weakness and weight loss although he maintained a fairly good appetite in periods of remission. He first noted dyspnea, pedal edema and brownish discoloration of the skin (forehead and face) in October, 1946. Several months before admission a physician told him he had an enlarged spleen.

The patient appeared chronically ill, with evidence of marked weight loss. The abdomen was markedly protuberant. The temperature was 101°F., pulse 100, respirations 20, and blood pressure 130 mm. of mercury systolic and 80 mm. diastolic. A diffuse brownish pigmentation of the forehead and face was noted. There was discrete generalized lymphadenopathy. The liver and spleen were greatly enlarged, firm but non-tender, and there was flaring of the costal margins. The over-all liver dullness in the mid-clavicular line measured 25 cm., the splenic dullness in the anterior axillary line

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18 cm. There was no ascites. Aside from moderate pedal edema there were no other significant physical findings.

Laboratory data were as follows: The red blood cell count was 3.1 million per cu. mm. and the blood hemoglobin concentration was 8.2 Gm. per 100 cc. The packed red cell volume was 30 per cent, the mean corpuscular volume 96 cubic micra, mean corpuscular hemoglobin 26 micro micrograms and mean corpuscular hemoglobin concentration 27.3 per cent. The reticulocyte count was 4.4 per cent. Examination of the blood smear showed excessive rouleaux formation, anisocytosis and poikilocytosis. The white blood cell count was 4,000 per cu. mm., with a differential count of 35 per cent metamyelocytes, 31 segmented neutrophils, 29 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils. Subsequent blood counts showed from 3,000 to 4,000 white blood cells with 2 to 8 per cent plasma cells. The coagulation and bleeding times were normal and the prothrombin time matched the normal control diluted to 30 per cent with physiologic saline. The blood sedimentation rate was 29 mm. in one hour (Wintrobe). The blood Kahn was negative. Serum agglutination studies for typhoid "O" and "H," paratyphoid "A" and "B," brucella, heterophils antibody and Proteus OX-19 were negative. Blood chemistry analyses included a markedly positive formol gel reaction, total serum protein of 9.8 Gm. per 100 cc. with 7.4 Gm. of globulin and 2.4 Gm. of albumin. The thymol turbidity reaction showed 40.5 units and the cephalin-flocculation test was reported as 3 plus in forty-eight hours.

The urinalysis showed a specific gravity of 1.021, negative tests for sugar and albumin and a rare white blood cell in the urinary sediment. Stool specimens contained Hymenolopsis nana and Trichuris trichiura. The spinal fluid pressure and dynamics were normal, total protein 26 mg. per cent, sugar 64 mg. per cent, globulin slightly increased, Kolmer-Wassermann negative and colloidal gold curve 5554210000.

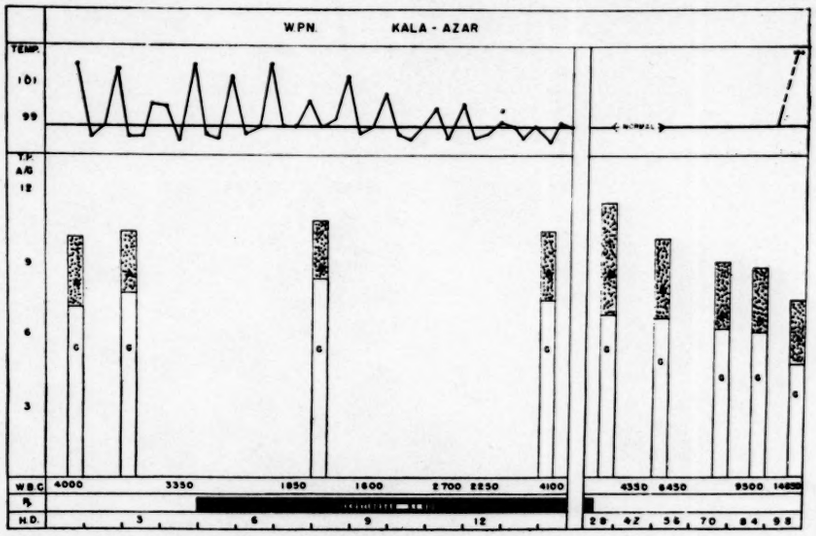


FIG. 1. Outline of the temperature, protein studies and leukocyte counts in a case of kala-azar.

Leishmania donovani were demonstrated in bone marrow and lymph node biopsies.

Following the establishment of a diagnosis of kala-azar, an intravenous dose of 0.2 Gm. ethylstibamine (neostibosan) was administered. Thereafter a daily dose of 0.3 Gm. was given intravenously for seventeen days (total dosage of 5.0 Gm.). There was no change in the fever until the twelfth day of therapy when the patient's temperature returned to normal. He was given a regular hospital diet and no other therapy. Subsequent white blood cell counts and blood protein studies are shown in Figure 1. The patient remained in the hospital for forty-eight days. During this time there was a gradual improvement and the liver and spleen decreased in size.

In February, 1948, the patient was re-admitted with uncomplicated pneumococcal lobar pneumonia. At that time the pigmentation on his face and forehead had cleared completely. The liver and spleen had returned to normal size and he had gained 25 pounds in weight. It

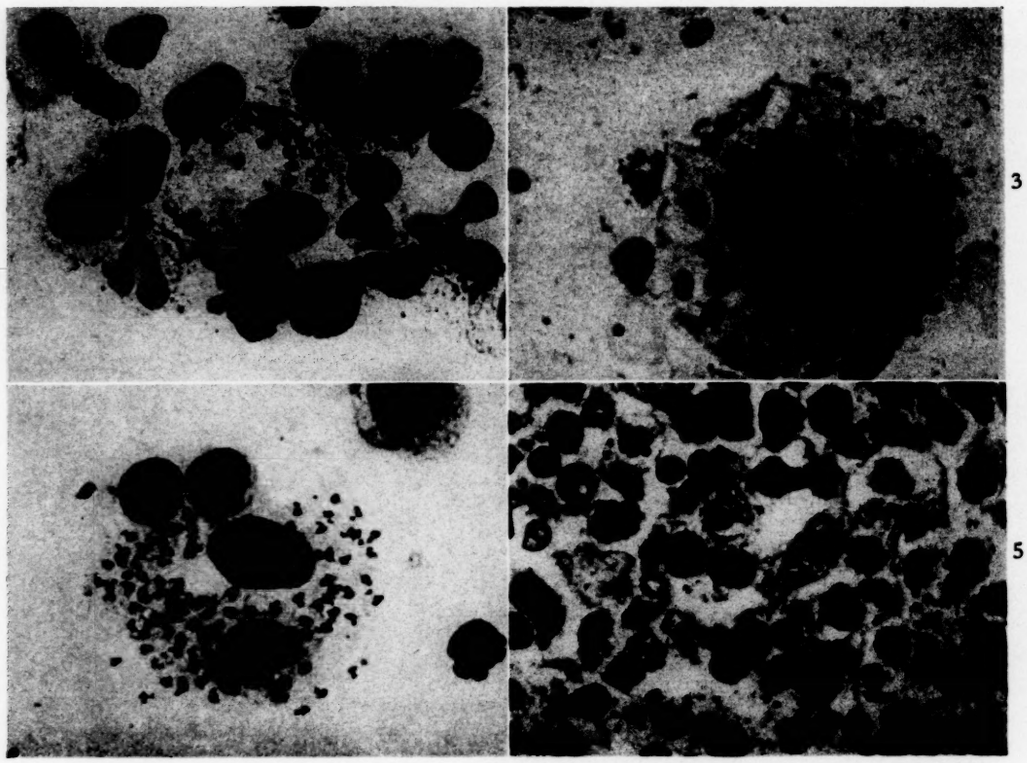


FIG. 2. Wright's stained serum spread of bone marrow showing Leishmania donovani engulfed by a macrophage.
FIG. 3. Higher magnification of macrophage in bone marrow containing Leishmania donovani. With Wright's stain the parasites show pale blue cytoplasm, dark purple nucleus and brilliant dot-like kinetoplast. Two extracellular parasites appear at upper left.
FIG. 4. Wright's stained serum spread of lymph node showing macrophage filled with parasites.
FIG. 5. Histologic section of lymph node stained with phyloxine-methylene blue showing parasites appearing as inclusion bodies in the cytoplasm of a macrophage.

is of interest to note that he had a leukocytosis of 14,650 on this admission. He was discharged asymptomatic and appeared entirely recovered when last seen in April, 1948.

Sternal bone marrow was obtained by surgical trephine and aspiration and two lymph nodes were removed from the epitrochlear region. Serum spreads were prepared from small portions of the curetted marrow and stained with Wright's stain, Giesma and Papanicolaou's stain. Numerous Leishmania donovani were demonstrated in the cytoplasm of macrophages, metamyelocytes and occasionally in segmented neutrophils in all preparations. (Figs. 2 and 3.) It is estimated from the differential and total cell counts[10] shown in Table 1 that 22,560 parasitized cells were present per cu. mm. of marrow. Smears made from heparinized blood aspirated from the marrow showed only a rare parasitized cell. Many parasites were found extracellularly appearing as small "torpedo" forms. Serum spreads, made from scrapings of the cut surface of the lymph node and stained with Wright's stain, revealed many parasitized macrophages.

Histologic preparations of bone marrow and lymph node were fixed in Zenker's solution with 5 per cent acetic acid and stained with phyloxine methylene blue. In the preparations the parasites appeared much smaller than in serum spreads of the bone marrow but could be recognized under oil immersion as small dot-like inclusion bodies in the cytoplasm of macrophages. (Figs. 4 and 5.) The bone marrow showed generalized hyperplasia of both myeloid and erythroid elements. The megakaryocytes were markedly increased but only a few appeared to be producing platelets. This finding has been described by Cartwright.[11] The most striking abnormality was the large number of plasma cells (15.8 per cent) and parasitized macrophages (3.2 per cent). It is interesting that more neutrophils were parasitized than macrophages, but in the former the morphology of the parasite was distorted. The differential bone marrow count is shown in Table 1.

TABLE I
HEMATOLOGIC FINDINGS IN BONE MARROW

	Curetted Marrow	Heparinized Sinusoidal Blood
	per cu. mm.	per cu. mm.
Total nucleated cell count	705,000	14,000
Myeloid leukocytes	305,970	
Nucleated erythrocytes	177,660	
Macrophages and monocytes	56,400	
Plasma cells	111,390	
Lymphocytes	38,775	
Megakaryocytes	14,805	
	705,000	
Macrophages containing parasites	22,560	
Neutrophils containing parasites	31,020	
Reticulocytes, per cent	14	
Erythroid-myeloid ratio	1 to 1:7	

	No.	Per cent	Total per cent
Differential cell count (1,000 cells):			
Reticulum cells	32	3.2	
Myeloblasts	34	3.4	
Promyelocytes	59	5.9	
Neutrophilic myelocytes	75	7.5	
Eosinophilic myelocytes	14	1.4	
Neutrophilic juveniles (16 parasitized)	114	11.4	
Neutrophilic bands (22 parasitized)	64	6.4	
Neutrophilic segmenters (6 parasitized)	32	3.2	
Eosinophils	10	1.0	43.4
Monocytes	14	1.4	
Macrophages (32 parasitized)	66	6.6	8.0
Pronormoblasts	4	0.4	
Basophilic normoblasts	83	8.3	
Polychromatophilic normoblasts	139	13.9	
Orthochromic normoblasts	26	2.6	25.2
Plasma cells	158	15.8	15.8
Lymphocytes	55	5.5	5.5
Megakaryocytes	21	2.1	2.1
Totals	1,000 cells	100.0	100.0

The architecture of the lymph node had been largely destroyed and in the section studied only one small germinal center could be identified. Numerous plasma cells were present in the medullary cords and there were many large mononuclear macrophages containing an abundant eosinophilic cytoplasm. Within the cytoplasm of these cells small basophilic inclusion bodies, surrounded by a clear zone, were identified.



FIG. 6. Motile, flagellated forms of the parasite stained with brilliant cresyl blue from fourteen-day culture on NNN medium.

Smears of leukocytic cream were examined and an extremely rare parasite was found in the cytoplasm of segmented neutrophils.

Cultures on Nicolle-Novy-MacNeal medium[1] were made from the button of bone marrow, curetted marrow, heparinized sinusoidal blood, a macerated lymph node and peripheral blood drawn immediately following biopsy. Leptomenas forms were demonstrated in all cultures from the tenth to the fourteenth day, with the exception of peripheral blood cultures which remained sterile. (Fig. 6.)

COMMENT

Kala-azar is prevalent throughout the world's tropical and sub-tropical zones but is most common along the Mediterranean Sea, Central Africa, India, Burma and China. The etiologic agent is Leishmania donovani, a paratozoal organism of the family trypanosomidae. This organism can be cultured on NNN medium and grows as a flagellated protozoa. In the cells of the reticuloendothelial system, however, it appears as a round, ovoid body measuring 2 to 5 micra in diameter.

The phlebotomus sandfly is generally considered to be the vector of kala-azar. The incubation period varies from a few

days to eighteen months.[12] The characteristics of the disease are chills, fever, generalized malaise, pigmentation of the skin, enlargement of the liver and spleen, and progressive loss of weight. The principal laboratory findings are leukopenia and hyperglobulinemia. The disease is most frequently confused with malaria. The high remittent fever and splenic enlargement common to malaria and kala-azar may make a differential diagnosis difficult. Many patients suffering from kala-azar have received antimalarial treatment on a purely empiric basis.

The diagnosis of kala-azar may be confirmed by the demonstration of the organism in bone marrow or lymph nodes by smear, culture or hamster inoculation. Splenic puncture[13] is commonly employed in many countries, but is not recommended because of the hazards involved.[14,15] The rapid formol gel reaction is not diagnostic of kala-azar but is an indication of hyperglobulinemia which is characteristic of the disease. It is of interest that the spinal fluid in this case showed no elevation of total protein.

Our bone marrow studies conform with those of Cartwright, Chung and Chang,[11] and those of Rachmilewitz, Braun and DeVries.[16] The high degree of parasitization of bone marrow cells is especially striking.

It is noted that the laboratory findings of hyperglobulinemia, plasmatocytosis of the bone marrow and excessive rouleau formation, considered characteristic of multiple myeloma, are found consistently in kala-azar. This coincidence of findings is the rationale for the treatment of multiple myeloma with stilbamidine as recently reported by Snapper.[17]

It is quite possible that many cases of kala-azar will be found in veterans who served in endemic areas. Confirmatory laboratory tests are not beyond the scope of most clinical laboratories. Once the diagnosis of kala-azar is proven, the results of therapy are gratifying and the prognosis changes from a mortality of 90 to 95 per cent without treatment to 2 to 5 per cent with specific antimony compounds.

SUMMARY

This report presents an instance of kala-azar occurring in a veteran of the North African, Sicilian and Italian campaigns. He had been treated as a case of malaria for over two years before the proper diagnosis was established. A detailed study of a bone marrow biopsy is included to demonstrate the high incidence of parasitized cells in the reticuloendothelial system and to emphasize the diagnostic value of this procedure.

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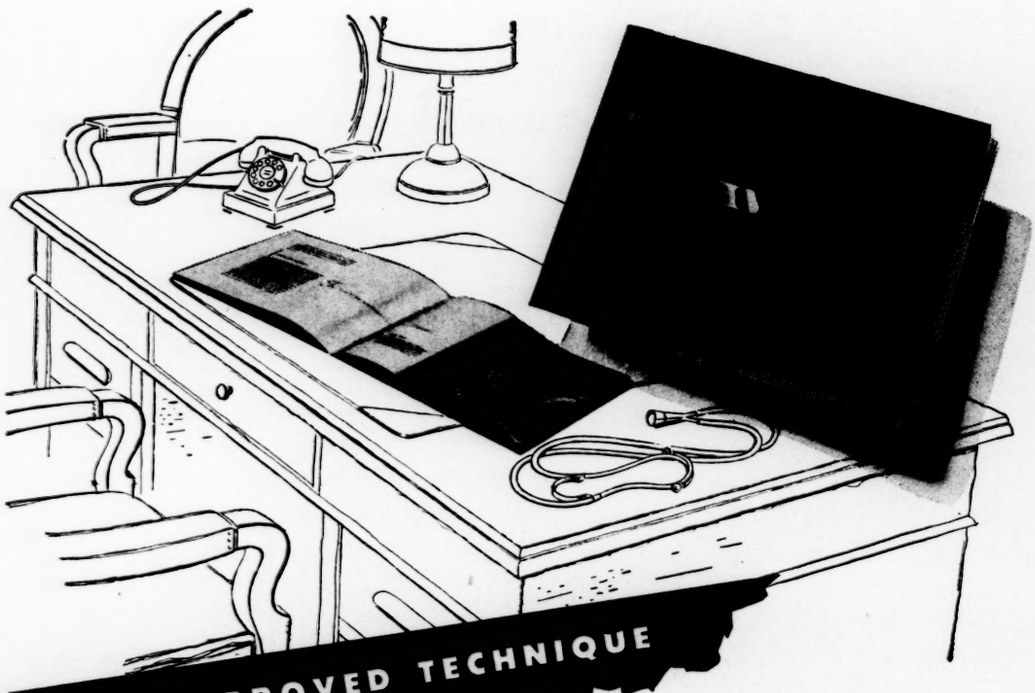
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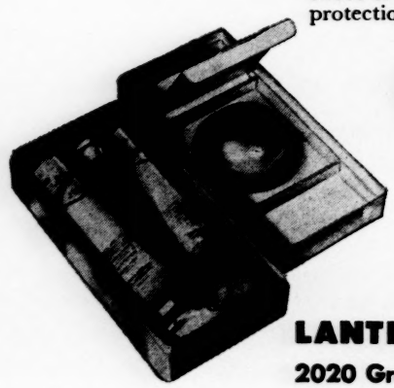
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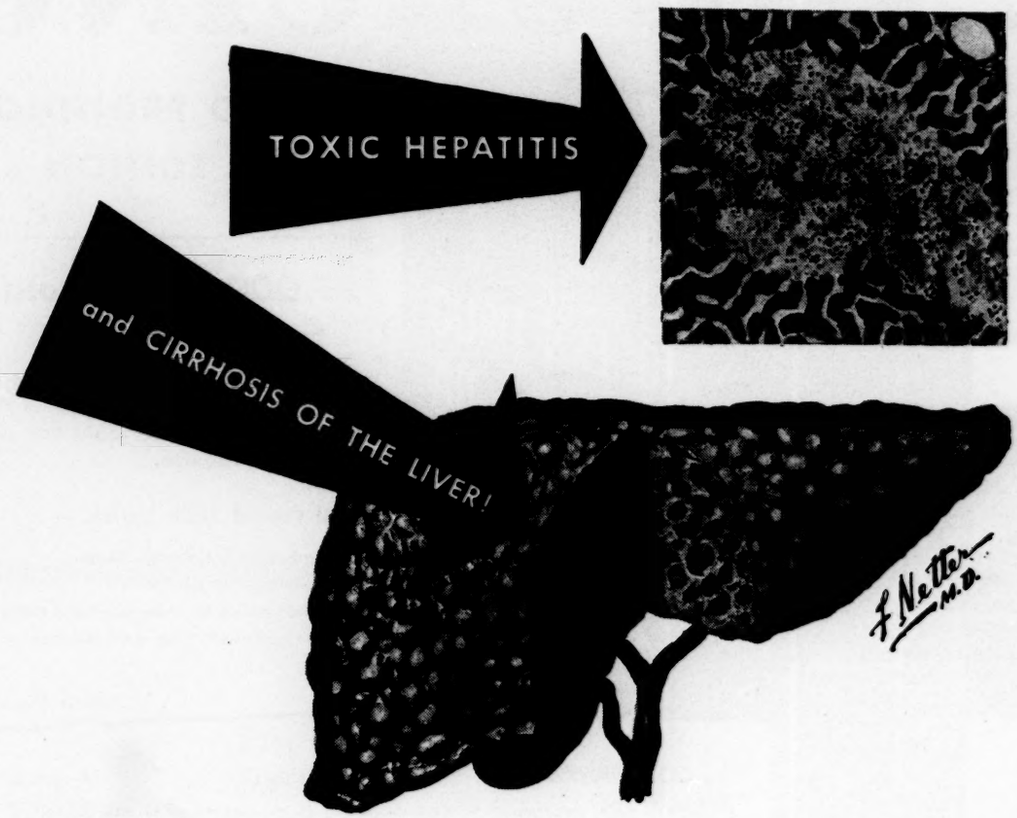
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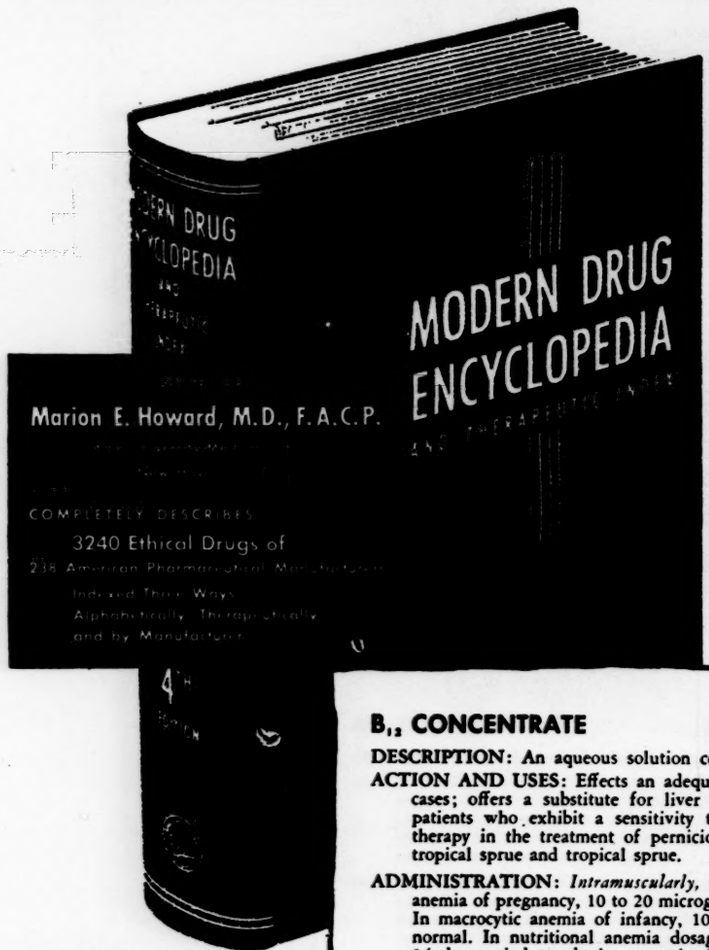
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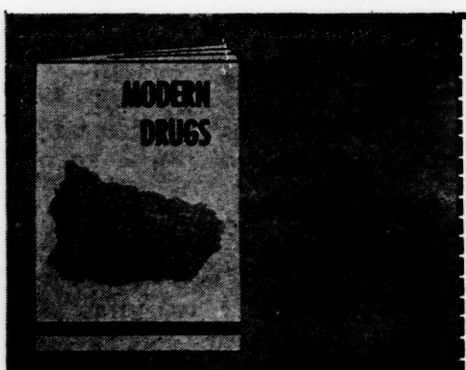
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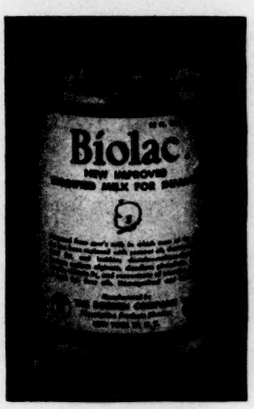
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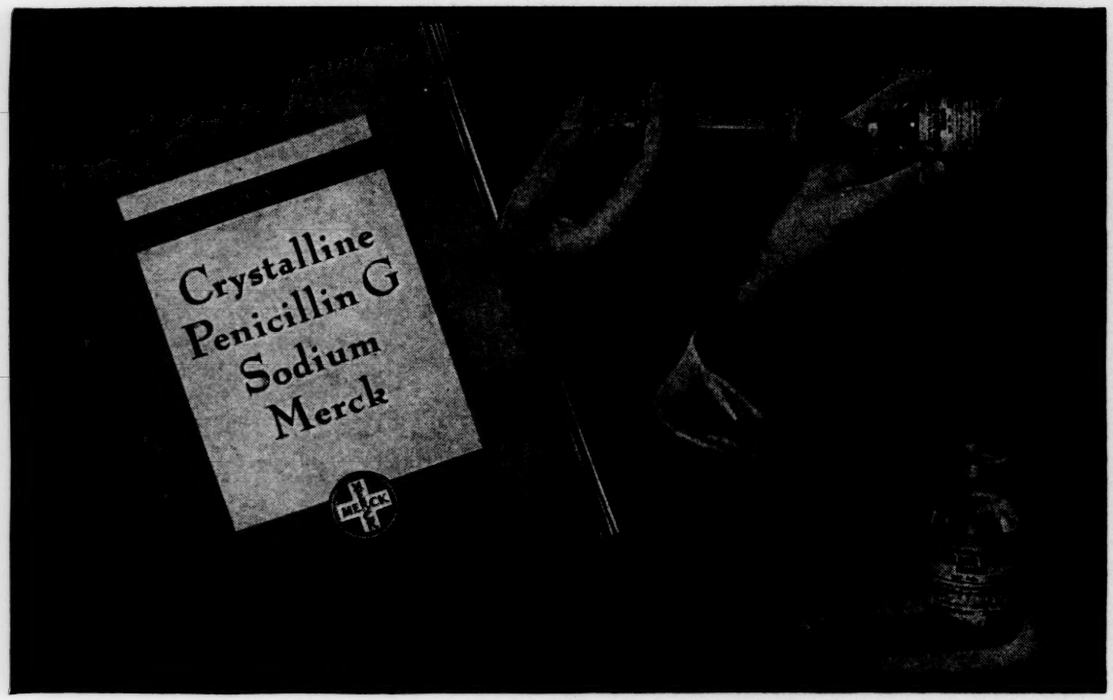
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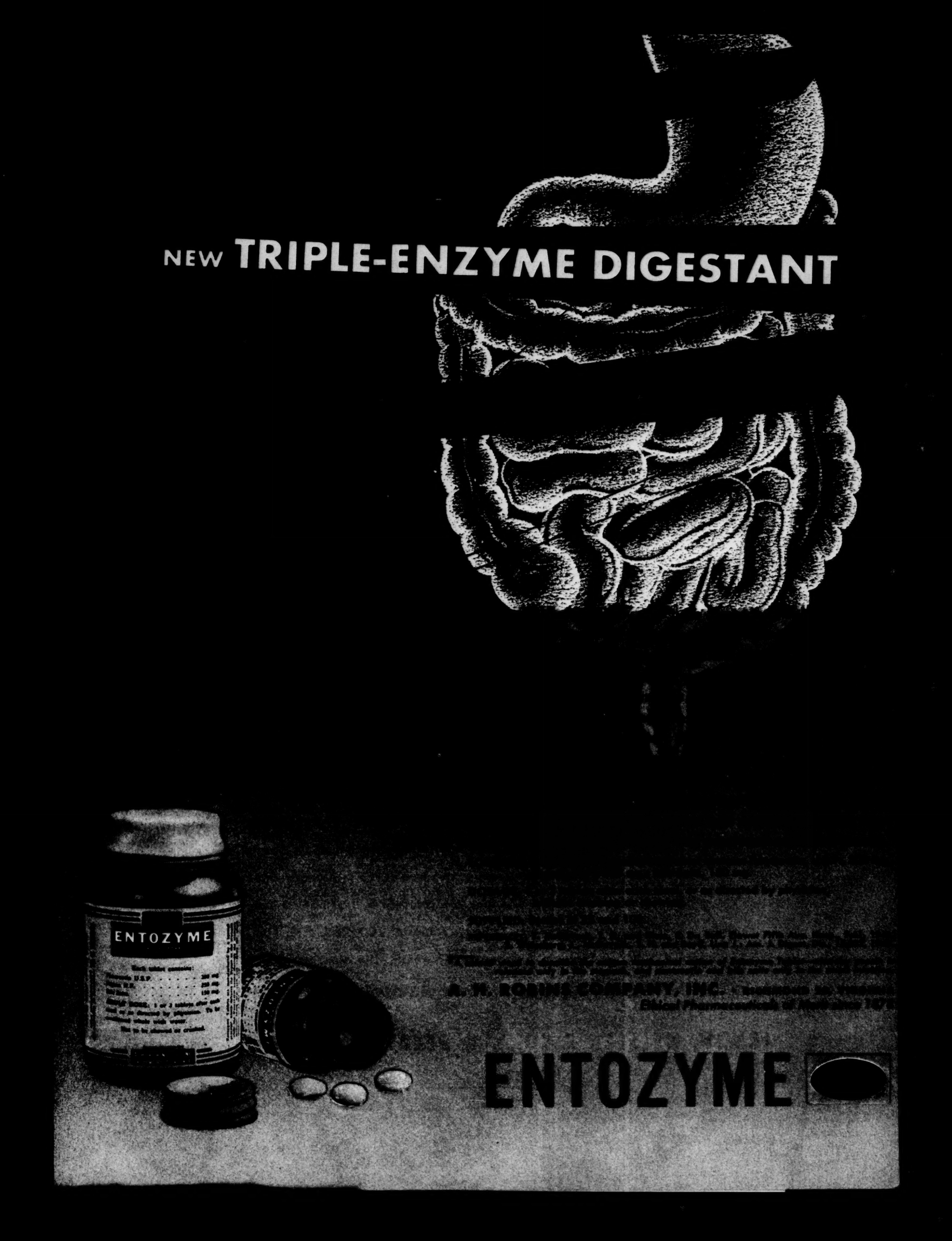
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Gill, A. M.: Proc. Roy. Soc. Med. 39:517, 1946.

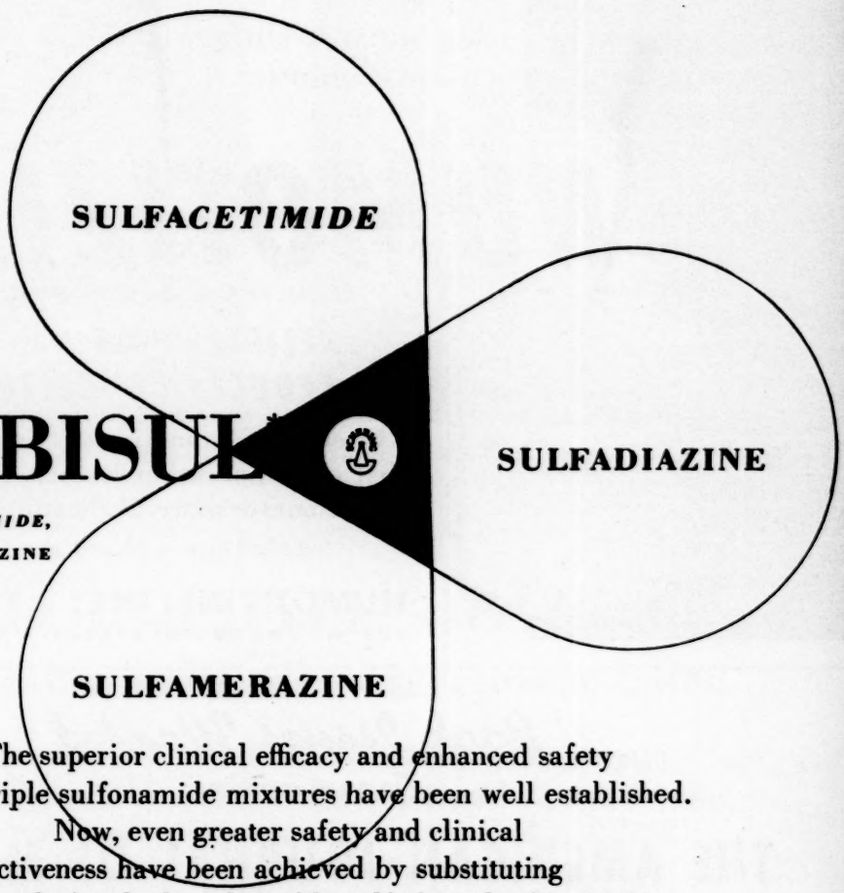
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1. Lehr, D.: To be published.

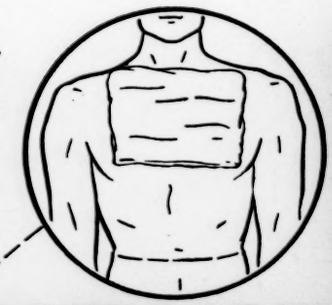
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*BOEHME, E. J.	The Treatment of Chronic Leg Ulcers	The Lahey Clinic Bulletin, 4:242 (1946)
BOWERS, WARNER F.	Chlorophyll in Wound Healing and Suppurative Disease	Amer. J. Surgery, LXXIII:37 (1947)
CADY, Jos. B. and MORGAN, W. S.	Treatment of Chronic Ulcers with Chlorophyll	Amer. J. Surgery, LXXV:4 (1948)
CARPENTER, E. B.	Chlorophyll Therapy in 127 Cases of Chronic Osteomyelitis and Ulcers	Amer. J. Surgery, 77:162(1949)
JOHNSON, HAROLD M.	Dermatologic evaluation...	Arch. Dermat. & Syph. 57:348 (1948)
LANGLEY, W. D. and MORGAN, W. S.	Chlorophyll in the Treatment of Dermatoses	Penn. Med. Journal, Vol. 51; No. 1 (1948)

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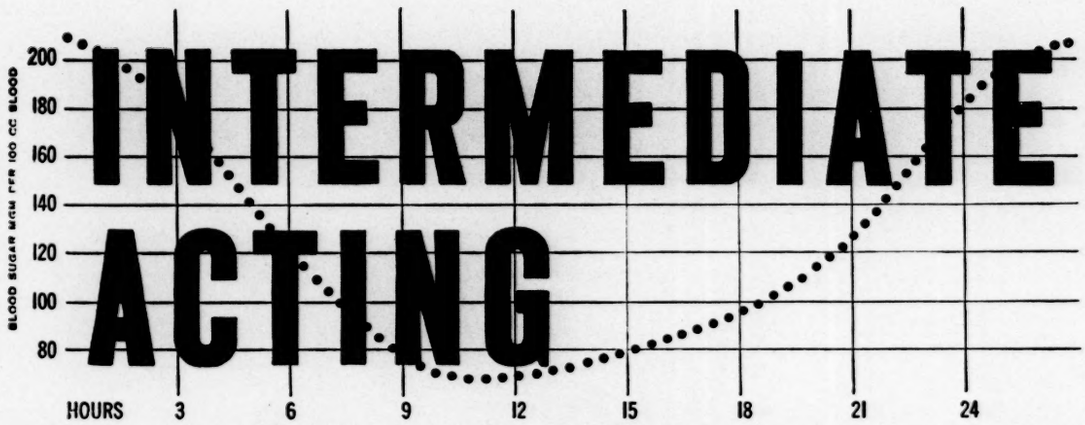
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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. Ibid Proc. Am. Diabetes Assn. 8:37, 1948.

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